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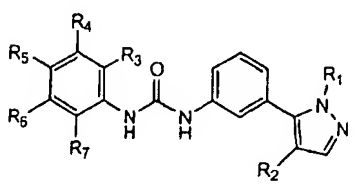
(54) Title: PROCESS OF MAKING PHENYLPYRAZOLES USEFUL AS SELECTIVE $5HT_{2A}$ MODULATORS AND INTERMEDIATES THEREOF



(I)

(57) Abstract: The present invention relates to a process for making certain selective $5HT_{2A}$ modulators of Formula (I) and the intermediates thereof: Formula (I) wherein R_1-R_7 are described. Compounds of Formula (I) are useful in the prophylaxis or treatment of $5HT_{2A}$ mediated diseases, such as, $5HT_{2A}$ mediated platelet aggregation, asthma, agitation, degenerative diseases of the CNS and the like.

PROCESS OF MAKING PHENYLPYRAZOLES USEFUL AS SELECTIVE $5HT_{2A}$ MODULATORS AND INTERMEDIATES THEREOF

FIELD OF THE INVENTION

The present invention concerns a process for making certain selective $5HT_{2A}$ modulators for the 5-HT_{2A} receptor. In particular, the application concerns a process for making compounds of Formula (I), as disclosed herein below, which are useful in the prophylaxis or treatment of $5HT_{2A}$ mediated disorders.

BACKGROUND OF THE INVENTION

I. G protein-coupled receptors

G protein-coupled receptors share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane. The transmembrane helices are joined by strands of amino acids having a larger loop between the fourth and fifth transmembrane helix on the extracellular side of the membrane. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly with the amino terminus in the extracellular space. It is thought that the loop joining helices five and six, as well as, the carboxy terminus, interact with the G protein. Currently, Gq, Gs, Gi and Go are G proteins that have been identified.

Under physiological conditions, G protein-coupled receptors exist in the cell membrane in equilibrium between two different states or conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response.

A receptor may be stabilized in an active state by an endogenous ligand or an exogenous agonist ligand. Recent discoveries such as, including but not exclusively limited

to, modifications to the amino acid sequence of the receptor provide means other than ligands to stabilize the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

II. Serotonin receptors

Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein-coupled receptors. Serotonin is thought to play a role in processes related to learning and memory, sleep, thermoregulation, mood, motor activity, pain, sexual and aggressive behaviors, appetite, neurodegenerative regulation, and biological rhythms. Not surprisingly, serotonin is linked to pathophysiological conditions such as anxiety, depression, obsessive-compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism, and neurodegenerative disorders. With respect to an anti-psychotic treatment, approaches focused on the serotonin receptors, these types of therapeutics can generally be divided into two classes, the "typical" and the "atypical." Both have anti-psychotic effects, but the typicals also include concomitant motor-related side effects (extra pyramidal syndromes, *e.g.*, lip-smacking, tongue darting, locomotor movement, etc). Such side effects are thought to be associated with the compounds interacting with other receptors, such as the human dopamine D2 receptor in the nigro-striatal pathway. Therefore, an atypical treatment is preferred. Haloperidol is considered a typical anti-psychotic, and clozapine is considered an atypical anti-psychotic.

Serotonin receptors are divided into seven subfamilies, referred to as 5-HT1 through 5-HT7, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT2 subfamily is divided into three receptor subtypes: 5-HT2A, 5-HT2B, and 5-HT2C. The human 5-HT2C receptor was first isolated and cloned in 1987, and the human 5-HT2A receptor was first isolated and cloned in 1990. These two receptors are thought to be the site of action of hallucinogenic drugs. Additionally, antagonists to the 5-HT2A and 5-HT2C receptors are believed to be useful in treating depression, anxiety, psychosis, and eating disorders.

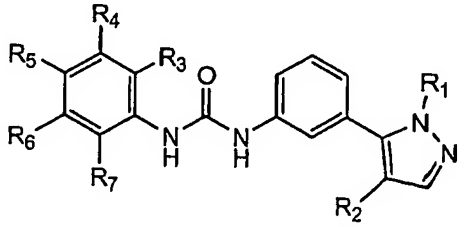
U.S. Patent Number 4,985,352 describes the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT1C receptor (now known as the 5-HT2C receptor). U.S. Patent Number 5,661,012 describes the isolation,

characterization, and expression of a functional cDNA clone encoding the entire human 5-HT2A receptor.

Mutations of the endogenous forms of the rat 5-HT2A and rat 5-HT2C receptors have been reported to lead to constitutive activation of these receptors (5-HT2A: Casey, C. *et al.* (1996) *Society for Neuroscience Abstracts*, 22:699.10, hereinafter "Casey"; 5-HT2C: Herrick-Davis, K., and Teitler, M. (1996) *Society for Neuroscience Abstracts*, 22:699.18, hereinafter "Herrick-Davis 1"; *and* Herrick-Davis, K. *et al.* (1997) *J. Neurochemistry* 69(3): 1138, hereinafter "Herrick-Davis-2"). Casey describes a mutation of the cysteine residue at position 322 of the rat 5-HT2A receptor to lysine (C322K), glutamine (C322Q), and arginine (C322R) which reportedly led to constitutive activation. Herrick-Davis 1 and Herrick-Davis 2 describe mutations of the serine residue at position 312 of the rat 5-HT2C receptor to phenylalanine (S312F) and lysine (S312K), which reportedly led to constitutive activation.

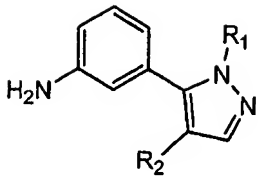
SUMMARY OF THE INVENTION

The present invention, in one aspect, provides a process for making compounds of Formula (**I**) useful in the prophylaxis or treatment of $5HT_{2A}$ mediated disorders, such as, $5HT_{2A}$ mediated platelet aggregation, asthma, agitation, degenerative diseases of the CNS, add-on therapy to Haloperidol for schizophrenia and other psychopathic disorders, as well as other diseases.



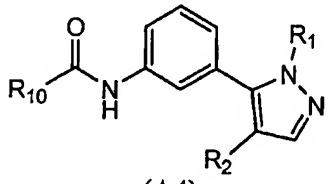
(**I**)

Some embodiments of the invention relate to the process for making compounds of Formula (**A5**) that are useful as intermediates in making compounds of Formula (**I**):



(A5)

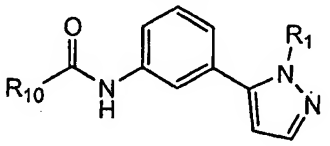
the process comprising hydrolyzing a compound of Formula (A4):



(A4)

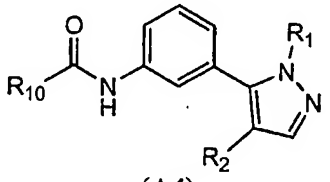
with an alkali metal hydroxide in a hydrolyzing solvent to yield a compound of Formula (A5); R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{10} is C_{1-6} alkyl. In some embodiments the alkali metal hydroxide is sodium hydroxide. In some embodiments the hydrolyzing solvent is aqueous ethanol. In some embodiments of the process for making a compound of Formula (A5) the hydrolyzing step is conducted between about 60°C to about 80°C.

In some embodiments the process for making a compound of Formula (A5) comprises the steps of halogenating a compound of Formula (A3):



(A3)

with a halogenating reagent in a halogenating solvent to yield a compound of Formula (A4):

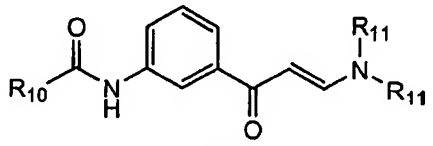


(A4) ;

and hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5); wherein R_{10} is C_{1-6} alkyl. In some embodiments the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide. In some embodiments the halogenating reagent is N-

bromosuccinimide and the halogenating solvent is N,N-dimethylformamide and the halogenating step is conducted between about 20°C to about 60°C. In some embodiments of the process for making a compound of Formula (**A5**) the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted between about 60°C to about 80°C.

In some embodiments the process for making a compound of Formula (**A5**) comprises the steps of cyclizing a compound of Formula (**A2**):

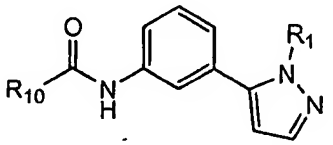


(**A2**)

with a compound of Formula (**B2**):

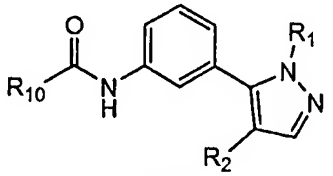
(**B2**)

the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (**A3**):



(**A3**) ;

halogenating a compound of Formula (**A3**) with a halogenating reagent in a halogenating solvent to yield a compound of Formula (**A4**);

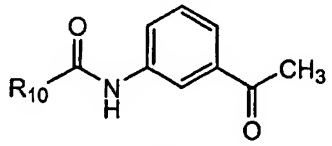


(**A4**) ;

and hydrolyzing a compound of Formula (**A4**) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (**A5**); wherein R_1 is C_{1-2} alkyl; R_{10} is C_{1-6} alkyl; and R_{11} is C_{1-3} alkyl. In some embodiments the process further comprises a cyclizing acid in the cyclizing step. In some embodiments the cyclizing acid is hydrochloric acid. In some embodiments the compound of Formula (**B2**) is methyl

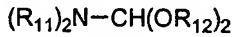
hydrazine. In some embodiments the cyclizing solvent is methanol. In some embodiments the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide, the halogenating solvent is N,N-dimethylformamide, and the halogenating step is conducted between about 20°C to about 60°C. In some embodiments the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted between about 60°C to about 80°C.

In some embodiments the process for making a compound of Formula (**A5**) comprises the steps of condensing a compound of Formula (**A1**):



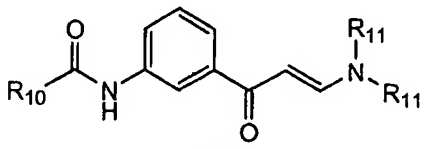
(**A1**)

with a compound of Formula (**B1**):



(**B1**)

the condensing step is optionally conducted in an condensing solvent to yield a compound of Formula (**A2**):

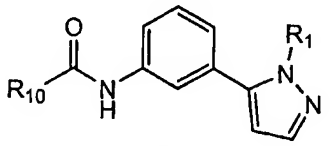


(**A2**) ;

cyclizing a compound of Formula (**A2**) with a compound of Formula (**B2**):

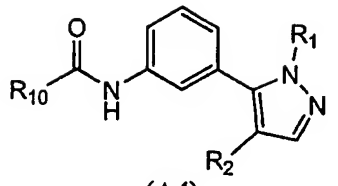
(**B2**)

the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (**A3**):



(**A3**) ;

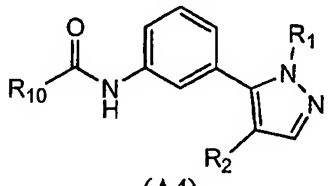
halogenating a compound of Formula (**A3**) with a halogenating reagent in a halogenating solvent to yield a compound of Formula (**A4**);



(A4) ;

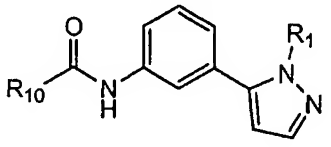
and hydrolyzing a compound of Formula (**A4**) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (**A5**); wherein R_1 is C_{1-2} alkyl; R_{10} is C_{1-6} alkyl; R_{11} is C_{1-3} alkyl; and R_{12} is C_{1-6} alkyl or alkylaryl; or both R_{12} groups together form a 5 or 6 membered heterocyclic ring. In some embodiments the compound of Formula (**B1**) is *N,N*-dimethylformamide dimethyl acetal. In some embodiments the condensing solvent is ethanol and the condensing step is conducted at a temperature of about 25°C to about 95°C. In some embodiments the condensing step is conducted at a temperature of about 70°C to about 80°C. In some embodiments the process further comprises a cyclizing acid in the cyclizing step and the cyclizing acid is hydrochloric acid. In some embodiments the compound of Formula (**B2**) is methyl hydrazine and the cyclizing solvent is methanol. In some embodiments the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide, the halogenating solvent is N,N-dimethylformamide, and the halogenating step is conducted between about 20°C to about 60°C. In some embodiments the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted between about 60°C to about 80°C.

Some embodiments of the invention include a process for making a compound of Formula (**A4**):



(A4)

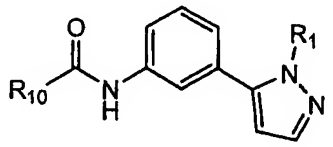
the process comprising the steps of halogenating a compound of Formula (**A3**):



(A3)

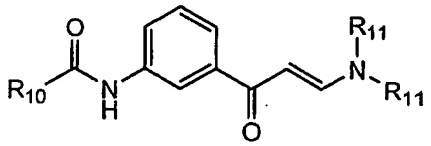
with a halogenating reagent in a halogenating solvent to yield the compound of Formula (**A4**); wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{10} is C_{1-6} alkyl. In some embodiments the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide. In some embodiments the halogenating reagent is N-bromosuccinimide and the halogenating solvent is N,N-dimethylformamide. In some embodiments the halogenating step is conducted between about 20°C to about 60°C.

Some embodiments of the invention include a process for making a compound of Formula (**A3**):



(**A3**)

the process comprising the steps of cyclizing a compound of Formula (**A2**):



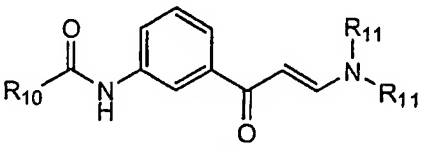
(**A2**)

with a compound of Formula (**B2**):

(**B2**) ;

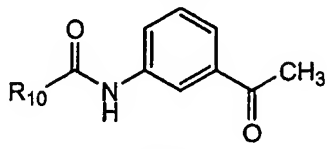
the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (**A3**); wherein R_1 is C_{1-2} alkyl; R_{10} is C_{1-6} alkyl; and R_{11} is C_{1-3} alkyl. In some embodiments the process further comprises a cyclizing acid in the cyclizing step. In some embodiments the cyclizing acid is hydrochloric acid. In some embodiments the compound of Formula (**B2**) is methyl hydrazine. In some embodiments the cyclizing solvent is methanol.

Some embodiments of the invention include a process for making a compound of Formula (**A2**):



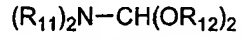
(**A2**)

the process comprising the steps of condensing a compound of Formula (**A1**):



(**A1**)

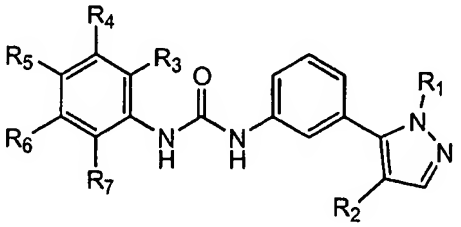
with a compound of Formula (**B1**):



(**B1**)

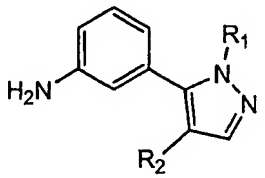
the condensing step is optionally conducted in an condensing solvent to yield a compound of Formula (**A2**); wherein R_{10} is C_{1-6} alkyl; R_{11} is C_{1-3} alkyl; and R_{12} is C_{1-6} alkyl or alkylaryl; or both R_{12} groups together form a 5 or 6 membered heterocyclic ring. In some embodiments the compound of Formula (**B1**) is *N,N*-dimethylformamide dimethyl acetal. In some embodiments the condensing solvent is ethanol and the condensing step is conducted at a temperature of about 25°C to about 95°C.

Some embodiments of the invention relate to a process for making a compound of Formula (**I**):



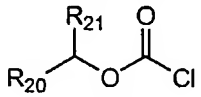
(**I**)

the process comprising a step of reacting a compound of Formula (**A5**):



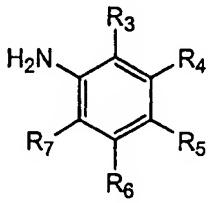
(**A5**)

with a substituted alkyl chloroformate of Formula (**B6**):



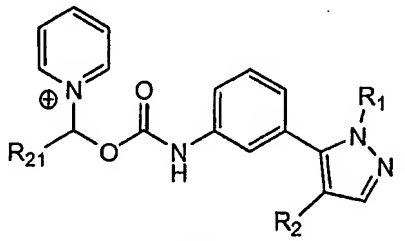
(**B6**)

and an organic base in a non-reactive solvent to give an intermediate; the intermediate is subsequently involved in a coupling with a compound of Formula (**A8**):



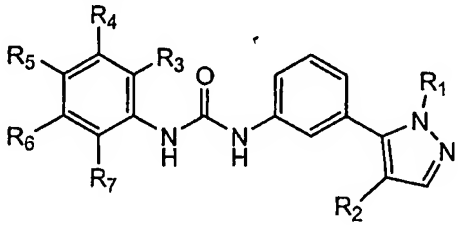
(A8)

to yield a compound of Formula (**I**); wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one R_3, R_4, R_5, R_6 and R_7 is not H; R_{20} is a Cl, Br, I, mesylate or tosylate; and R_{21} is a C_1-C_8 alkyl;. In some embodiments the organic base is pyridine. In some embodiments the non-reactive solvent is methylene chloride. In some embodiments the intermediate has the Formula (**C2**):



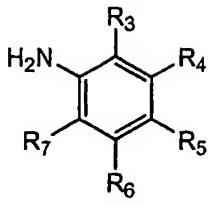
(C2)

In an alternative manner, some embodiments of the invention relate to a process for making a compound of Formula (**I**):



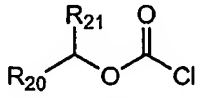
(I)

the process comprising a step of reacting a compound of Formula (**A8**):



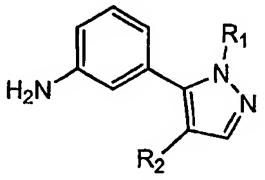
(A8)

with a substituted alkyl chloroformate of Formula (B6):



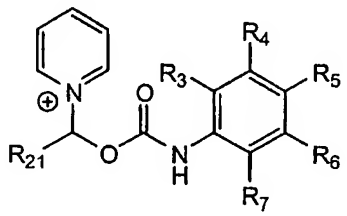
(B6)

and an organic base in a non-reactive solvent to give an intermediate. The intermediate is subsequently coupled with a compound of Formula (A5):



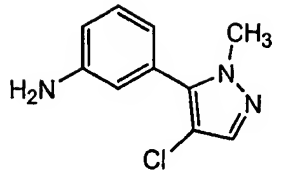
(A5)

wherein R_1 and R_2 have the same meaning as described above; to yield the compound of Formula (I); wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one R_3, R_4, R_5, R_6 and R_7 is not H; R_{20} is a Cl, Br, I, mesylate or tosylate; and R_{21} is a C_1-C_8 alkyl. In some embodiments the process the organic base is pyridine. In some embodiments the non-reactive solvent is methylene chloride. In some embodiments of the process the intermediate is Formula (C4):

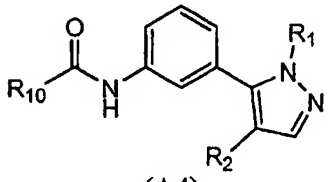


(C4)

Some embodiments of the invention include a compound of the Formula:



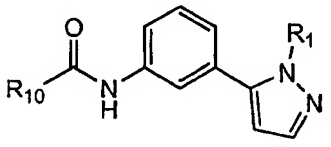
Some embodiments of the invention include a compound of Formula (**A4**):



(A4)

wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{10} is C_{1-6} alkyl. In some embodiments R_1 and R_{10} are both CH_3, and R_2 is Br.

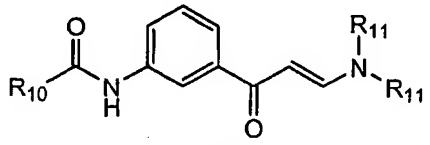
Some embodiments of the invention include a compound of Formula (**A3**):



(A3)

wherein R_1 is C_{1-2} alkyl; and R_{10} is C_{1-6} alkyl. In some embodiments R_1 and R_{10} are both CH_3.

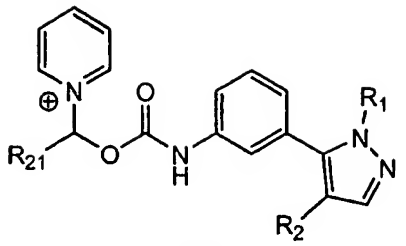
Some embodiments of the invention include a compound of Formula (**A2**):



(A2)

wherein R_{10} is C_{1-6} alkyl; and R_{11} is C_{1-3} alkyl. In some embodiments R_{10} and R_{11} are both CH_3.

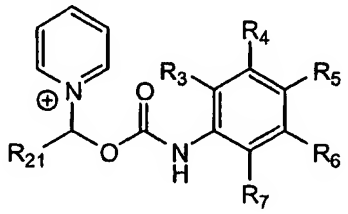
Some embodiments of the invention include a compound of Formula (**C2**):



(C2)

wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{21} is C_1-C_8 alkyl. In some embodiments a compound of Formula (**C2**) are when R_1 is CH_3; R_2 is Br; and R_{21} is CH_3.

Some embodiments of the invention include a compound of Formula (**C4**):

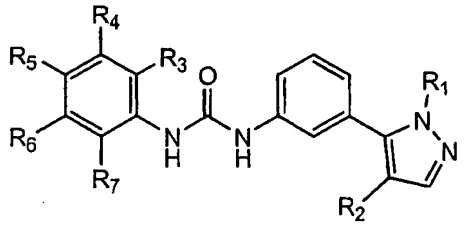


(C4) ;

wherein R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; and R_{21} is C_1-C_8 alkyl. In some embodiments compounds of Formula (C3) are when R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, F or Cl; and R_{21} is CH_3.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the invention encompasses a process for making compounds of Formula (**I**) useful in the prophylaxis or treatment of $5HT_{2A}$ mediated disorders:



(I)

wherein:

R_1 is C_{1-2} alkyl;

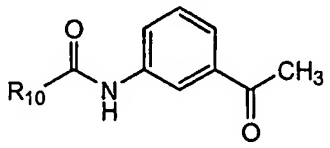
R_2 is Cl or Br;

R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H;

comprising the steps of:

Step (i)

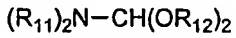
Condensing a compound of Formula (**A1**):



(A1)

wherein R_{10} is C_{1-6} alkyl;

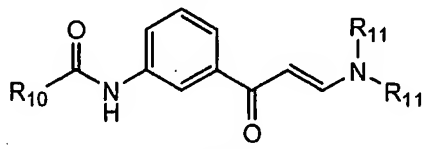
with a compound of Formula (**B1**):



(B1)

wherein R_{11} is C_{1-3} alkyl; and R_{12} is C_{1-6} alkyl or alkylaryl; or both R_{12} groups together form a 5 or 6 membered heterocyclic ring;

the condensing step is optionally conducted in a condensing solvent to yield a compound Formula (**A2**). A compound of Formula (**A2**) is also referred to as an enaminone and is of the formula:

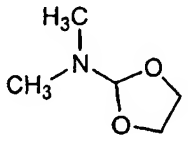


(A2) ;

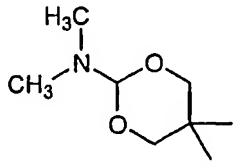
In reference to Formula (**A1**), the acyl group, formed by the R_{10} group together with the carbonyl, serves as an amino protecting group in step (i), the resulting group is more commonly referred to an amide group. A variety of groups for R_{10} may be utilized provided that the resulting acyl group bearing the R_{10} group can be removed as described in step (iv). R_{10} may be selected from, but not limited to, the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, pentyl, neopentyl and hexyl. Preferably R_{10} is methyl.

A variety of *N,N*-dialkylformamide acetals of the Formula (**B1**) may be used in step (i). For example, R_{11} may be selected from, but not limited to, the group consisting of methyl, ethyl, propyl and iso-propyl. Preferably R_{11} is methyl. When R_{12} is alkyl, then R_{12} may be selected from, but not limited to, the group consisting of methyl, ethyl,

propyl, iso-propyl, n-butyl, *tert*-butyl and neopentyl. Preferably R_{12} is methyl. Examples of *N,N*-dialkylformamide acetals of Formula (**B1**) when R_{12} is alkyl include for example, *N,N*-dimethylformamide dimethyl acetal, *N,N*-dimethylformamide diethyl acetal, *N,N*-dimethylformamide dipropyl acetal, *N,N*-dimethylformamide diisopropyl acetal, *N,N*-dimethylformamide dibutyl acetal, *N,N*-dimethylformamide di-*tert*-butyl acetal and *N,N*-dimethylformamide dineopentyl acetal. When R_{12} is cycloalkyl, then R_{12} may be selected from, but not limited to, the group consisting of cyclopentyl or cyclohexyl. One example of an *N,N*-dialkylformamide acetal of Formula (**B1**) when R_{12} is cycloalkyl includes *N,N*-dimethylformamide dicyclohexyl acetal. When R_{12} is C_{1-2} alkylaryl, then R_{12} is selected from, but not limited to, the group consisting of benzyl, 1-phenylethyl and 2-phenylethyl. One example of an *N,N*-dialkylformamide acetal of the Formula (**B1**) when R_{12} is C_{1-2} alkylaryl includes, *N,N*-dimethylformamide dibenzyl acetal. When both R_{12} groups together form a 5 or 6 membered heterocyclic ring, then the *N,N*-dialkylformamide acetal of Formula (**B1**) may be selected from, but not limited to, the group consisting of *N,N*-dimethylformamide ethylene acetal and *N,N*,5,5-tetramethyl-1,3-dioxan-2-amine and are represented by the following structure:

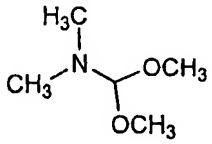


N,N-dimethylformamide ethylene acetal



N,N,5,5-tetramethyl-1,3-dioxan-2-amine.

Preferably, R_{11} and R_{12} are both methyl and the compound is represented by the following structure:



N,N-dimethylformamide dimethyl acetal.

The condensing solvent may optionally be present or absent. In the instance that the condensing solvent is absent then the *N,N*-diallkylformamide dialkylacetal of Formula (**B1**) serves both as a reactant in condensation step (i) and as the solvent. When

a condensing solvent is present, the solvent is selected from, but not limited to, the group consisting of methanol, ethanol, butanol, pentanol, 1-propanol and 2-propanol. Preferably the condensing solvent is present and preferably the solvent is ethanol.

The condensing step is conducted at a temperature between about 25°C to about 95°C. Preferably the condensing step is conducted at a temperature between about 50°C to about 85°C and most preferably between about 70°C to about 80°C.

Generally, the molar ratio of an acetophenone of Formula (**A1**) to an *N,N*-dialkylformamide dialkyl acetal of Formula (**B1**) is such that the *N,N*-dialkylformamide dialkyl acetal is used in excess. Typically, when the condensing solvent is absent, then the molar ratio of the acetophenone to the *N,N*-dialkylformamide dialkyl acetal is in a ratio of 1 to at least about 1. Stated differently, when the solvent is absent, the *N,N*-dialkylformamide dialkyl acetal is present in at least about 1 molar equivalent compared to the acetophenone. Any amount of *N,N*-dialkylformamide dialkyl acetal in excess of this about 1 molar equivalent may serve the role of a solvent or some other function, such as, to increase the rate of the reaction, improve mechanical manipulation (i.e., stirring, mixing) and the like. When the condensing solvent is present, the molar ratio of an acetophenone of Formula (**A1**) to a *N,N*-dialkylformamide dialkyl acetal of Formula (**B1**) is typically about 1:1 to about 1:3, and preferably the ratio is between about 1:1.1 to about 1:2. The presence of the *N,N*-dialkylformamide dialkyl acetal outside these ranges in excess may be determined by methods known in the art.

Step (ii)

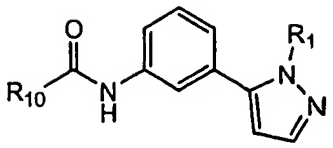
Cyclizing a compound of Formula (**A2**) with a compound of Formula (**B2**). Compounds of Formula (**B2**) are also referred to as an alkylhydrazine and are of the formula:

$$R_1—NHNH_2$$

(B2)

wherein R_1 is C_{1-2} alkyl;

the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (**A3**);



(A3)

Preferably, the alkylhydrazine is methyl hydrazine and R_1 is methyl. The cyclizing solvent may optionally be present or absent. In the instance that the cyclizing solvent is absent then the alkylhydrazine of Formula (**B2**) serves both as a reactant in the cyclization step (**ii**) and as the solvent. When a cyclizing solvent is present, the solvent is selected from, but not limited to, the group consisting of methanol, ethanol, butanol, pentanol, 1-propanol and 2-propanol. Preferably the cyclizing solvent is present and preferably the solvent is methanol.

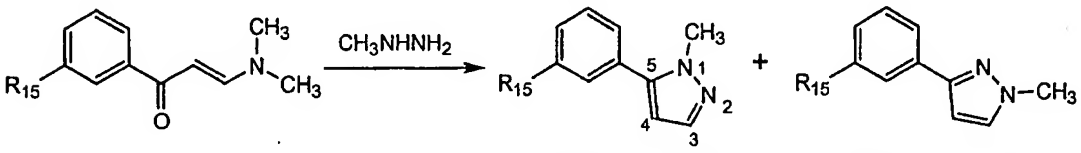
In some embodiments, the cyclizing step (**ii**) further comprises the addition of a cyclizing acid, selected from, but not limited to, the group consisting of hydrochloric acid, hydrobromic acid, acetic acid and trifluoroacetic acid; the cyclizing acid is preferably hydrochloric acid. In some embodiments the molar ratio of the alkylhydrazine and cyclizing acid is typically between the range of about 1:0.1 to about 1:20; in another embodiment the molar ratio of the alkylhydrazine and cyclizing acid is between about 1:05 to about 1:12 and preferably the range is between about 1:1 to about 1:8.

Generally, the molar ratio of the enaminone of Formula (**A2**) to alkylhydrazine of Formula (**B2**) is such that the alkylhydrazine is present in excess. Typically, when the cyclization solvent is absent, then the molar ratio of the enaminone of Formula (**A2**) to the compound of Formula (**B2**) is in a ratio of 1 to at least 1. Stated differently, when the solvent is absent, the alkylhydrazine is present in at least about 1 molar equivalent compared to the enaminone of Formula (**A2**). Any amount of alkylhydrazine in excess of this about 1 molar equivalent serves as the role of a solvent or some other function, such as, to increase the rate of the reaction, improve mechanical manipulation (i.e., stirring, mixing) and the like. When the cyclization solvent is present, in general the molar ratio of the enaminone to alkylhydrazine is between about 1:1 to about 1:3; another range is typically between about 1:1 to about 1:1.5; and preferably the range is between about 1:1 to about 1:1.2. The cyclizing step is conducted at a temperature between about –25°C to about 60°C, preferably the cyclizing step is conducted at a temperature between about

–10°C to about 25°C.

Some embodiments of the invention show a high degree of regiospecificity in the cyclization; **TABLE 1** illustrates the ratio of 2-methylpyrazole to 1-methylpyrazole.

TABLE 1



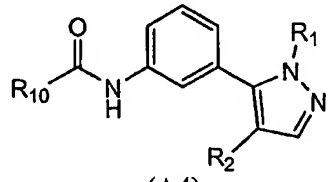
1-Methylpyrazole 2-Methylpyrazole

R_{15}	Temperature (°C)	RATIO 1-Methylpyrazole	2-Methylpyrazole
NO_2-	0 to RT	84	16
CH_3CONH- *	0 to RT	86	14
CH_3CONH- **	0 to RT	91	9

* 3.2 eq. of HCl and 1.16 eq of methylhydrazine were used in the reaction.
** 6.0 eq of HCl and 1.12 eq of methylhydrazine were used in the reaction.
See Examples for additional information, *infra*.

Step (iii)

Halogenating a compound of Formula (**A3**) with a halogenating reagent in a halogenating solvent to yield a compound of Formula (**A4**);



(**A4**)

In one embodiment when R_2 is Br, the halogenating reagent may be selected from the available reagents known in the art, such as, for example, N-bromosuccinimide (i.e., NBS), 1,3-dibromo-5,5-dimethylhydantoin, pyridinium tribromide ($pyrHBr_3$) and the like; preferably, N-bromosuccinimide is the halogenating reagent for when R_2 is Br. This step is superior to the use of bromine (i.e., Br_2) in the bromination step. For example, the use of bromine in CH_2Cl_2 required large stoichiometric excess of bromine and excessive reaction times. Even under these conditions the reaction gave selectivity difficulties as observed by the presence of significant amounts of unconverted starting material and

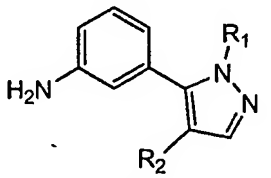
dibrominated by products. Furthermore, the use of bromine CH_2Cl_2 gave heterogeneous reaction mixtures and reaction monitoring difficulties.

Based in part on the discovery of the brominating reagent, the halogenating reagent is preferably N-chlorosuccinimide (i.e., NCS) for when R_2 is Cl.

Generally, the molar ratio of a compound of Formula (**A3**) to halogenating reagent is typically in the range varying between a ratio of about 1:0.9 to about 1:1.1; preferably the range is between about 1:0.95 to about 1:1.05. The use of excess halogenating reagent may lead to the incorporation of multiple bromines into the product. The halogenating solvent is a suitable polar solvent such as *N,N*-dimethylformamide (i.e., DMF), methylsulfoxide, acetonitrile, ethyl acetate, methylene chloride and the like; preferably the solvent is DMF. One beneficial feature in the use of a water soluble halogenating solvent such as DMF, is the particular ease in separating the resulting product of step (**iii**) from the solvent. To illustrate this point, where DMF and NBS were used in the halogenating step (**iii**), the resulting product was isolated by the addition of water. After the addition, the product was allowed to crystallize from the halogenating mixture to yield the desired compound in high yield and purity, 92% and 99.2% respectively. A similar result was seen in the example of DMF and NCS, *infra.*

Typically the halogentating step is conducted at a temperature between about 10°C to about 80°C, preferably the halogenating step is conducted at a temperature between about 20°C to about 60°C.

(**iv**) Hydrolyzing a compound of Formula (**A4**) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (**A5**):



(**A5**)

Suitable bases for this step include, for example, alkali metal hydroxides such as lithium hydroxide, sodium hydroxide or potassium hydroxide. Preferably, the alkali metal hydroxide is sodium hydroxide.

Generally, the molar ratio of a compound of Formula (**A4**) to alkali metal hydroxide is typically in the range varying between a ratio of about 1:1 to about 1:10;

another range is typically between about 1:3 to about 1:8; preferably the range is between about 1:4 to about 1:6.

The aqueous hydrolyzing solvent is a mixture of water with a suitable polar solvent selected from the group consisting of tetrahydrofuran (THF), methanol, ethanol, 1-propanol, 2-propanol, butanol and pentanol; included are mixtures thereof. Preferably the polar solvent is ethanol. The amount of water present is typically determined by the amount necessary to dissolve the corresponding alkali metal hydroxide. The hydrolyzing step is conducted at a temperature between about 20°C to about 100°C. Preferably the condensing step is conducted at a temperature between about 50°C to about 85°C and most preferably between about 60°C to about 80°C.

Surprisingly, acid hydrolysis using, for example, 2 equivalents of HCl in boiling ethanol, resulted in both the desired deacetylation leading to a compound of Formula (**A5**) and also to at least one undesirable side-reaction. One presumed side-reaction under acidic conditions is the disproportionation of certain compounds of Formula (**A4**). Several products resulting from disproportionation were identified as aniline derivatives containing either no bromine atoms or 2 bromine atoms. These compounds not only contributed to the impurity profile for this step but also removed material that would otherwise be converted to product. Representative data comparing acidic and alkaline are shown in Examples, *infra.*

This problem was overcome by utilizing alkaline conditions as described herein. One representative example using alkaline conditions is in the deacetylation of 5-(3'-acetaminophenyl)-4-bromo-1-methyl-1*H*-pyrazole to 5-(3'-aminophenyl)-4-bromo-1-methyl-1*H*-pyrazole giving 95.9 % overall yield with no detectable side-products.

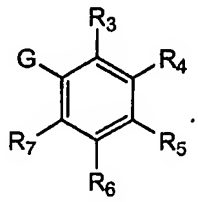
Urea Forming Steps

The following steps are alternatives to forming the urea moiety in compounds of the invention. In general, Step (**v**) may use a commercially available aryl isocyanate or one that can be prepared by known methods and coupled with the aniline of Formula (**A5**) to yield a compound of Formula (**I**). An analogous two-part step is described in Steps (**vi**) and (**vii**) in which the isocyanate is prepared (i.e., Step (**vi**)) from the aniline of Formula (**A5**) and subsequently coupled (i.e., Step (**vii**)) with the aniline of Formula

(A8). Step (viii) is yet another urea forming step. In this step, an aniline of Formula (A5) may be reacted with a substituted alkyl chloroformate in the presence of an organic base to give in intermediate that is subsequently coupled with an aniline of Formula (A8). This step may be modified, as illustrated in Step (ix) to give yet another urea forming step, namely, aniline of Formula (A8) may be reacted with a substituted alkyl chloroformate to give an intermediate that is reacted with an aniline of Formula (A5). The following sections provide additional details of these steps.

1. **Step (v)**

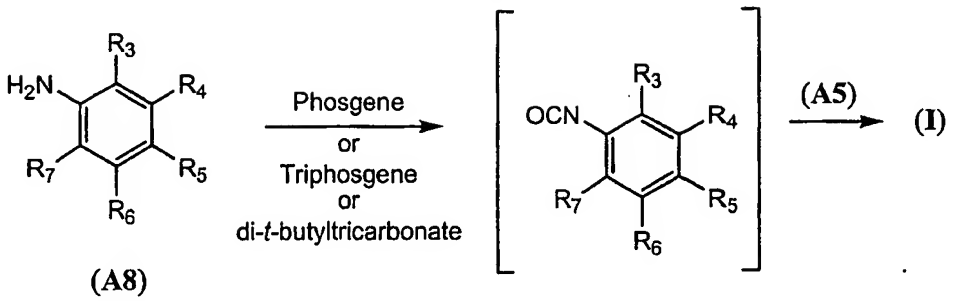
Coupling a compound of Formula (A5) with a compound of Formula (A6):



(A6)

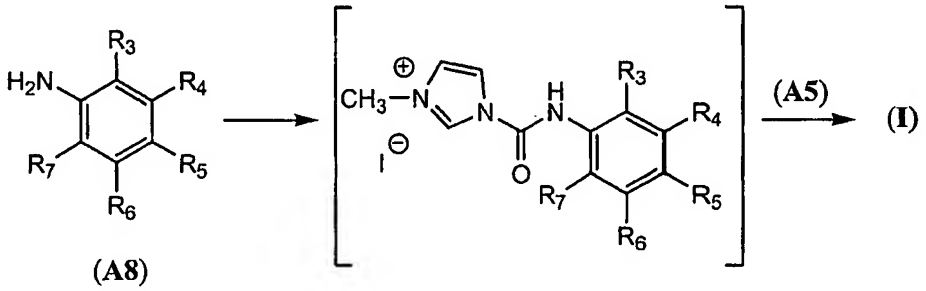
wherein R_3, R_4, R_5, R_6 and R_7 have the same definitions as described above; and G is an isocyanate or isocyanate equivalent group; the coupling step being conducted in a coupling solvent to give a compound of Formula (I).

A suitable G group in step (v) is an isocyanate (-N=C=O) or isocyanate equivalent. Isocyanates and isocyanate equivalents are well known in the art; many isocyanates are commercially available. For those isocyanates that are not commercially available, they may be readily prepared utilizing the corresponding anilines, for example, the use of phosgene (i.e., $Cl_2C=O$) or triphosgene [i.e., bis-trichloromethyl carbonate, $Cl_3COC(O)OCCl_3$] to generate the isocyanate *in situ* or isolated for subsequent use. Another procedure using di-*t*-butyltricarbonate generate isocyanates from anilines in a similar manner as described above has been reported by Peerlings et al. in *Tetrahedron Lett.* **1999**, *40*, 1021-1024. These procedures and others known in the art may give rise to useful isocyanates as illustrated in Scheme 1 below:



Scheme 1

Alternatively, isocyanate equivalents may also be used and prepared from the corresponding aniline by the sequential action of carbonyl diimidazole and methyl iodide in THF and acetonitrile respectively as described by Batey et al. in *Tetrahedron Lett.* **1998**, *39*, 6267-6270. This procedure may give rise to useful isocyanate equivalents as illustrated in the reaction scheme below:



Scheme 2

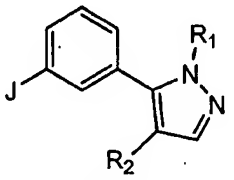
Generally, the molar ratio of a compound of Formula (**A5**) to a compound of Formula (**A6**) is typically in the range of varying between about 1:1 to about 1:1.5; preferably about 1:1 to about 1:1.2. The coupling solvent is a suitable non-reactive solvent such as *N,N*-dimethylformamide (i.e., DMF), methylsulfoxide, acetonitrile, ethyl acetate, methylene chloride and the like; preferably the solvent is methylene chloride. The coupling step (**v**) is typically conducted at a temperature between about 0°C to about 60°C; preferably the temperature is between about 10°C to about 45°C.

2. Step (vi)

An alternative process to step (**v**) is described below. This alternative embodiment comprises a compound of Formula (**A5**) that may be converted into a compound bearing an isocyanate or isocyanate equivalent in a manner described above.

This alternative embodiment comprises two steps identified as steps (**vi**) and (**vii**); these steps are specifically described, *infra*.

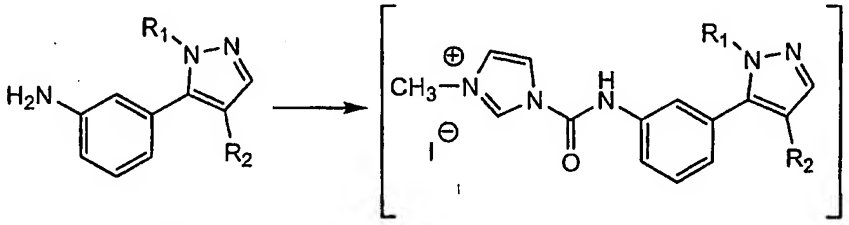
Reacting a compound of Formula (**A5**) with an isocyanate generating reagent in an isocyanate generating solvent to yield a compound of Formula (**A7**):



(**A7**)

wherein J is an isocyanate or isocyanate equivalent;

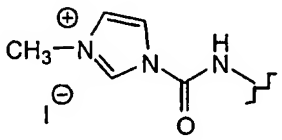
The isocyanate generating reagent may be selected from the available reagents known in the art including those described herein, such as, phosgene, triphosgene or di-*t*-butyltricarbonate, wherein the resulting product is of Formula (**A7**) and J is -N=C=O. An isocyanate generating reagent is also defined as forming a chemical species that reacts in a manner comparable to an isocyanate, such as the chemical species shown in brackets in Scheme 3 below:



(**A5**)

Scheme 3

In this example J is considered as an isocyanate equivalent and is represented by the Formula shown below:



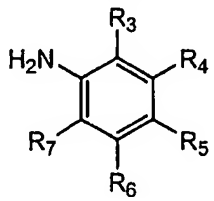
Generally, the molar ratio of a compound of Formula (**A5**) to an isocyanate generating reagent is typically in the range varying between about 1:1 to about 1:2; preferably about 1:1 to about 1:1.2. The isocyanate generating solvent is a suitable non-reactive solvent such as *N*,*N*-dimethylformamide (i.e., DMF), methylsulfoxide, acetonitrile, tetrahydrofuran (i.e., THF), ethyl acetate, methylene chloride, toluene and

the like; preferably the solvent is methylene chloride, acetonitrile, THF or toluene; and most preferably, the solvent is substantially free of water. The coupling step (**vi**) is typically conducted at a temperature between about -10°C to about 60°C; preferably the temperature is between about 10°C to about 50°C.

It is generally understood in the art that although the isocyanate or isocyanate equivalent may be isolated it may not always be necessary to do so and that this fact would be recognized by the artesian. Therefore, in certain instances the isocyanate or isocyanate equivalent may be generated *in situ* and reacted directly with the appropriate aniline without isolation.

Step (vii)

Coupling the compound of Formula (**A7**) with a compound of Formula (**A8**):



(**A8**)

wherein R_3, R_4, R_5, R_6 and R_7 have the same meaning as described herein, *supra*; the coupling step being conducted in a coupling solvent to give a compound of Formula (**I**).

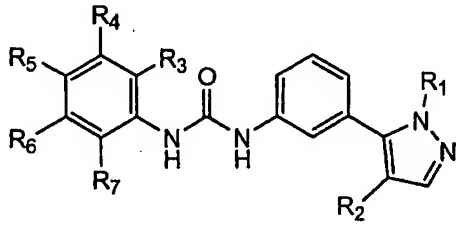
Generally, the molar ratio of a compound of Formula (**A7**) to a compound of Formula (**A8**) is typically in the range varying between about 1:1 to about 1:1.5; preferably about 1:1 to about 1:1.2. The coupling solvent is a suitable non-reactive solvent such as *N*,*N*-dimethylformamide (i.e., DMF), methylsulfoxide, acetonitrile, ethyl acetate, methylene chloride and the like; preferably the solvent is methylene chloride. The coupling step (**vii**) is typically conducted at a temperature between about 0°C to about 60°C; preferably the temperature is between about 10°C to about 50°C.

3. Step (viii)

Step (**viii**) is yet another urea forming step. This is an alternative process step to that of step (**v**), *supra*, to yield compounds of the inventions. This alternative embodiment comprises a compound of Formula (**A5**) that may be converted into a

compound bearing an isocyanate or isocyanate equivalent in a analogous manner as described above. This alternative embodiment comprises the making of an intermediate that may be isolated or directly coupled with a compound Formula (**A6**); this particular step is identified as step (**viii**) and is specifically described *infra.*

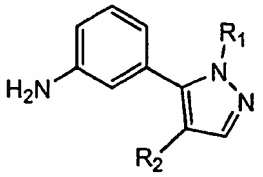
Some embodiments of the invention relate to a process for making a compound of Formula (**I**):



(**I**)

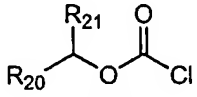
wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H. This process comprises the step of:

reacting a compound of Formula (**A5**):



(**A5**)

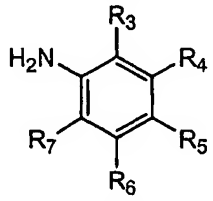
wherein R_1 and R_2 have the same meaning as described above, with a substituted alkyl chloroformate of Formula (**B6**):



(**B6**)

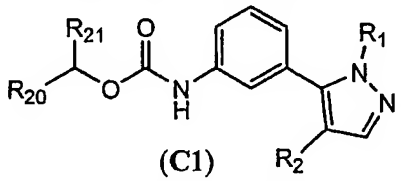
wherein R_{20} is a leaving group, such as, Cl, Br, I, mesylate, tosylate, and the like; and R_{21} is a C_1-C_8 alkyl; such as, methyl, ethyl, propyl, butyl, pentyl, isopropyl, nenopentyl, hexyl, octyl and the like; in the presence of an organic base; such as, pyridine, dimethylaminopyridine, piperidine, morpholine and the like. In some embodiments the organic base is pyridine. This step is conducted in a non-reactive solvent to give an intermediate. The non-reactive solvent is a suitable polar solvent, such as *N,N*-

dimethylformamide (i.e., DMF), methylsulfoxide, acetonitrile, ethyl acetate, tetrahydrofuran (i.e., THF), methylene chloride and the like; preferably the solvent is methylene chloride. The intermediate formed, may be isolated or subsequently used in a coupling reaction with a compound of Formula (**A8**):



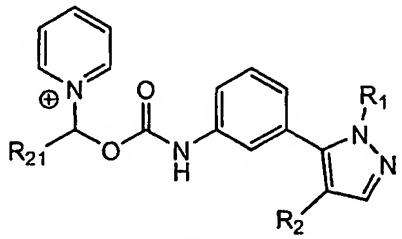
(A8)

wherein R_3-R_7 have the same meaning as described above, to yield a compound of Formula (**I**). The intermediate may have the structure of Formula (**C1**) shown below:



(C1)

where R_1, R_2 and R_{21} have the same definition as described *supra*. Intermediate (**C1**) may result from the addition of a compound of Formula (**A5**) to the substituted alkyl chloroformate. Another intermediate may have the structure of Formula (**C2**):



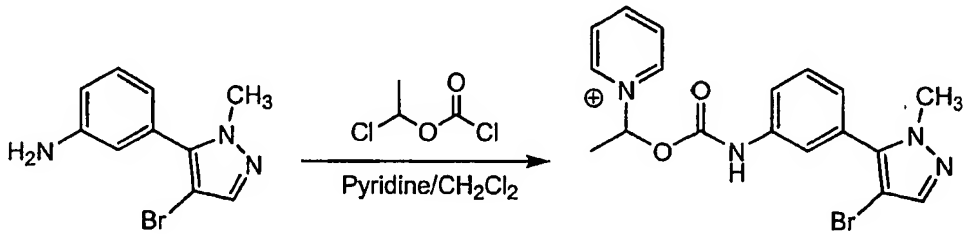
(C2)

where R_1, R_2 and R_{21} have the same definition as described *supra*. Intermediate (**C2**) may arise from displacement of the R_{20} leaving group by the organic base (i.e., pyridine) and subsequent addition of a compound of Formula (**A5**); or from the displacement of the R_{20} by the organic base of the intermediate (**C1**). Optionally, an additional organic base, such as one described *supra* for this step, may be used in reacting the intermediate with an aniline of Formula (**A5**).

Generally, the molar ratio of a compound of Formula (**A5**) to a substituted alkyl chloroformate of Formula (**B6**) is typically in the range varying between about 1:1 to

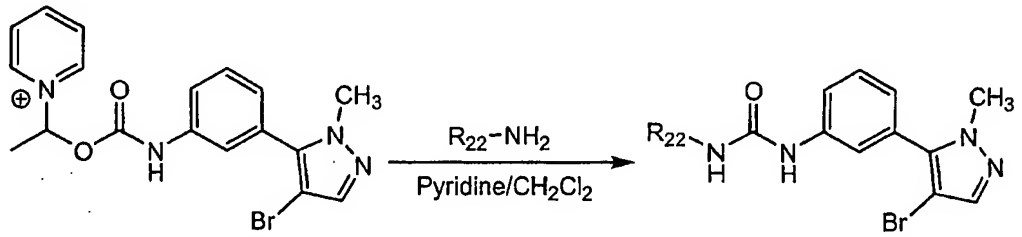
about 1:2; preferably about 1:1 to about 1:1.5. Step **(vii)** may be conducted at a temperature between about 0°C to about 60°C; preferably the temperature is between about 10°C to about 45°C.

By way of an example, when 5-(3-aminophenyl)-4-bromo-1-methylpyrazole **(5)** was treated with a substituted alkyl chloroformate, such as, 1-chloroethyl chloroformate a pyridinium salt **(28)** was isolated as shown below:



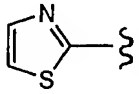
(5) **(28)**

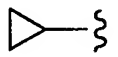
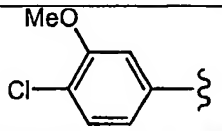
The resulting pyridinium salt **(28)**, when treated with a variety of amines, such as, isopropyl amine, 2-aminothiazole, cyclopropyl amine, 4-chloro-3-methoxyaniline, and the like, gave the coupled products, as illustrated in the reaction scheme below:



(28)

Representative examples are shown in the table below:

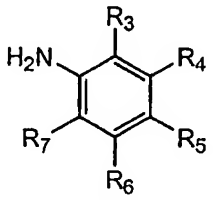
Compound No.	R
29	
30	

31	
32	

4. **Step (ix)**

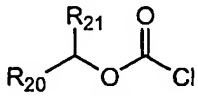
In an alternative but analogous manner to step (**viii**), step (**ix**) may be conducted using the aniline of Formula (**A8**) and treating it with a substituted alkyl chloroformate of Formula (**B6**) to generate an intermediate, which in turn may be coupled with a compound of Formula (**A5**) to yield a compound of Formula (**I**). Additional details of Step (**ix**) are specifically described *infra*.

This process comprises the step of reacting a compound of Formula (**A8**):



(**A8**)

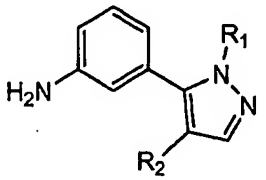
wherein R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; with a substituted alkyl chloroformate of Formula (**B6**):



(**B6**)

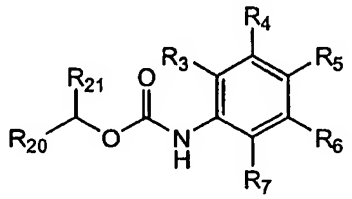
wherein R_{20} is a Cl, Br, I, mesylate or tosylate, and the like; and R_{21} is a C_1-C_8 alkyl, such as those examples described *supra*. This reaction is conducted in the presence of an organic base, such as, pyridine, dimethylaminopyridine, piperidine, morpholine and the like; in a non-reactive solvent to give an intermediate. In some embodiments, the organic base is pyridine. The non-reactive solvent can be one of the solvents described in step

(viii). Preferably the solvent is methylene chloride. The intermediate is subsequently involved in a coupling with a compound of Formula (A5):



(A5)

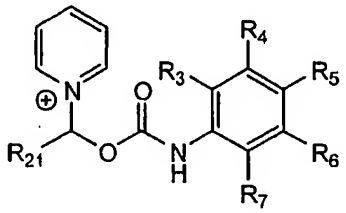
wherein R_1 is C_{1-2} alkyl; and R_2 is Cl or Br; to yield the compound of Formula (I). The intermediate may be represented by the structure shown below:



(C3)

wherein R_3, R_4, R_5, R_6, R_7, R_{20} and R_{21} have the same meaning as described, *supra*. Intermediate (C3) may result from the addition of a compound of Formula (A8) to the substituted alkyl chloroformate.

Another intermediate may have the structure of Formula (C4):



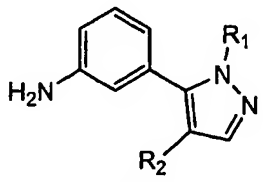
(C4) ;

wherein R_3, R_4, R_5, R_6, R_7, R_{20} and R_{21} also have the same meaning as described, *supra*. Intermediate (C4) may arise from displacement of the R_{20} leaving group by the organic base (i.e., pyridine) and subsequent addition of a compound of Formula (A8); or from the displacement of the R_{20} by the organic base of intermediate (C3).

Optionally, an additional organic base, such as one described *supra* for this step, may be used in reacting the intermediate with an aniline of Formula (A5).

Generally, the molar ratio of a compound of Formula (**A8**) to a substituted alkyl chloroformate Formula (**B6**) is typically in the range varying between about 1:1 to about 1:2; preferably about 1:1 to about 1:1.5. This step may be conducted at a temperature between about 0°C to about 60°C; preferably the temperature is between about 10°C to about 45°C.

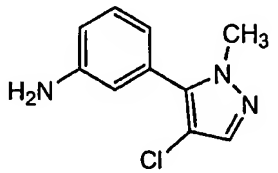
In a second aspect, the invention encompasses a process for making compounds that are useful as intermediates in the process for making compounds of Formula (**I**). One embodiment is a process for making a compound of Formula (**A5**):



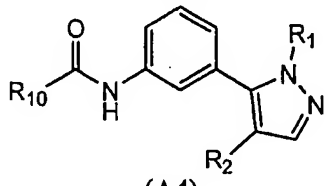
(**A5**)

wherein R_1 is C_{1-2} alkyl; and R_2 is Cl or Br. The steps for the making compounds of Formula (**A5**) are described, *supra*.

In a third aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (**I**) wherein the intermediate is of the following structure:



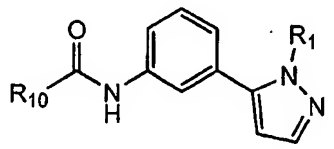
In a fourth aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (**I**) wherein the intermediate is of Formula (**A4**):



(**A4**)

wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{10} is C_{1-6} alkyl, preferably R_1 and R_{10} are both CH_3, and R_2 is Br.

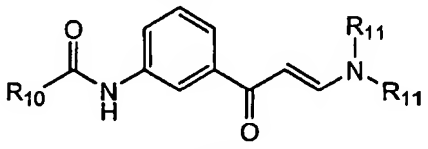
In a fifth aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (**I**) wherein the intermediate is of Formula (**A3**):



(A3)

wherein R_1 is C_{1-2} alkyl; and R_{10} is C_{1-6} alkyl, preferably R_1 and R_{10} are both CH_3.

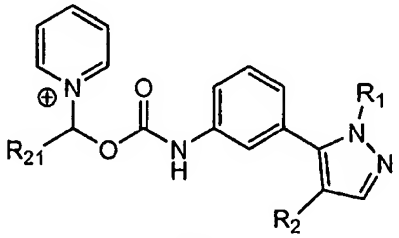
In a sixth aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (**I**) wherein the intermediate is of Formula (**A2**):



(A2)

wherein R_{10} is C_{1-6} alkyl; and R_{11} is C_{1-3} alkyl, preferably R_{10} and R_{11} are both CH_3.

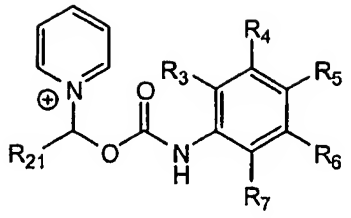
In a seventh aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (**I**) wherein the intermediate is of Formula (**C2**):



(C2)

wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{21} is C_1-C_8 alkyl. Preferably, R_1 is CH_3; R_2 is Br; and R_{21} is CH_3.

In an eighth aspect, the invention encompasses a useful intermediate in the making of compounds of Formula (**I**) wherein the intermediate is of Formula (**C4**):



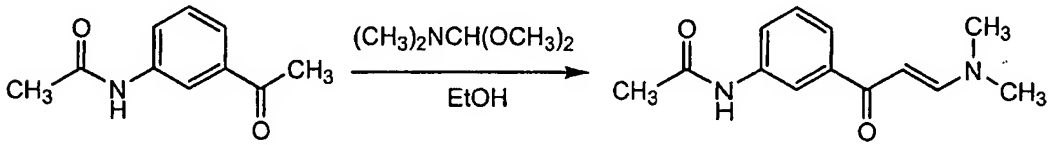
(C4) ;

wherein R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; and R_{21} is C_1-C_8 alkyl. Preferably, R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, F or Cl; provided that at least one is not H; and R_{21} is CH_3.

The invention is further illustrated in the following steps wherein preferred reactants are shown to more clearly demonstrate the process disclosed. In Scheme 4, R_1, R_{10} and R_{11} are each methyl; R_2 is bromo, R_3, R_4, R_6, R_7 are each hydrogen; and R_5 is chloro.

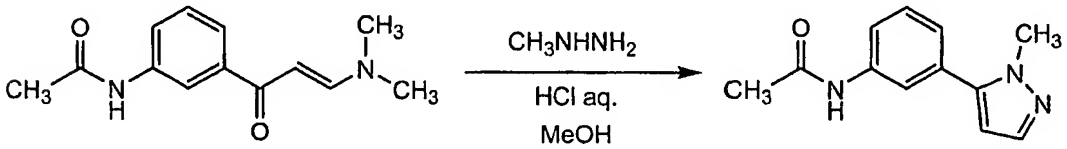
Scheme 4

Step (i)



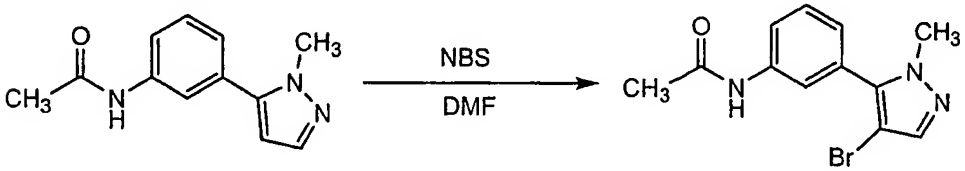
(1) (2)

Step (ii)



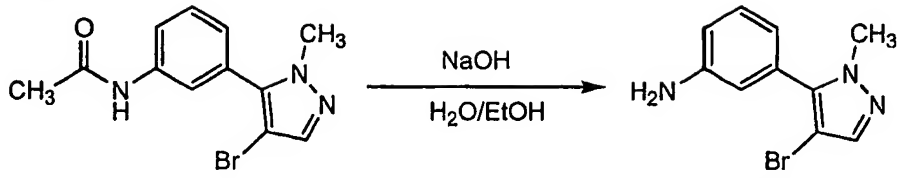
(2) (3)

Step (iii)



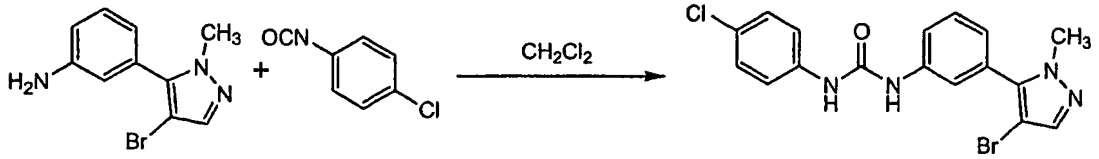
(3) (4)

Step (iv)



(4) (5)

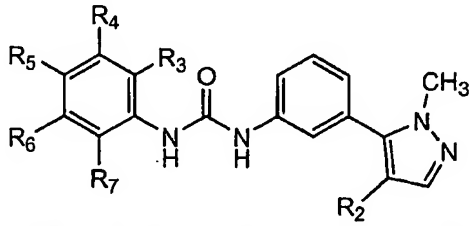
Step (v)



(5) (6) Compound **26**

Representative activities for the 5-HT_{2A} modulators of the present invention are shown in Table 1, *infra*; see Examples 1-4 for description:

TABLE 1



Compound No.	R_2	R_3	R_4	R_5	R_6	R_7	IC_{50} (nM) IP Accumlation
9	Cl	H	F	F	H	H	18
10	Cl	F	H	H	F	H	37
11	Cl	H	F	H	F	H	46
12	Cl	H	Cl	F	H	H	23
13	Cl	F	H	F	H	H	25

14	Cl	F	F	F	H	H	48
15	Cl	CF_3	H	F	H	H	158
16	Cl	H	CF_3	F	H	H	45
17	Br	F	H	F	H	H	14
18	Br	H	F	F	H	H	28
19	Br	H	F	H	F	H	79
20	Br	H	Cl	F	H	H	17
21	Br	CF_3	H	F	H	H	69
22	Br	H	CF_3	F	H	H	11
23	Br	F	F	F	H	H	19
24	Br	CF_3	H	Cl	H	H	34
25	Br	H	CF_3	Cl	H	H	27
26	Br	H	H	Cl	H	H	8
27	Br	H	H	F	H	H	6

DEFINITIONS

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control.

AGONISTS shall mean moieties that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

PARTIAL AGONISTS shall mean moieties which activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists.

ANTAGONIST shall mean moieties that competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. ANTAGONISTS do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

CANDIDATE COMPOUND shall mean a molecule (for example, and not limitation, a chemical compound) which is amenable to a screening technique.

COMPOSITION shall mean a material comprising at least two compounds or two components; for example, and not limitation, a Pharmaceutical Composition is a Composition.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity.

INHIBIT or **INHIBITING**, in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INVERSE AGONISTS shall mean moieties that bind the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

In addition to the foregoing beneficial uses for the modulators of 5HT2a receptor activity disclosed herein, the compounds disclosed herein are believed to be useful in the treatment of several additional diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include the following:

1. Antiplatelet Therapies (5HT2a mediated platelet aggregation):

Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or

stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

In a myocardial infarction (heart attack), the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 minutes), antiplatelets can reduce the damage to the heart.

A transient ischemic attack ("TIA" or "mini-stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation blood clots that cause first or second strokes.

Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly

irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the heart and traveling to the brain (embolism).

5HT2a receptors are expressed on smooth muscle of blood vessels and 5HT secreted by activated platelets causes vasoconstriction as well as activation of additional platelets during clotting. There is evidence that a 5HT2a inverse agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy. See Satimura, K, et al., Clin Cardiol **2002** Jan. 25 (1):28-32; and Wilson, H.C et al., Thromb Haemost **1991** Sep 2;66(3):355-60.

The 5HT2A inverse agonists disclosed herein provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limitation, the indications described above.

2. Asthma

It has been suggested that 5-HT (5-hydroxytryptamine) plays a role in the pathophysiology of acute asthma. See Cazzola, M. and Matera, M.G., TiPS, **2000**, 21, 13; and De Bie, J.J. et al., British J. Pharm., **1998**, 124, 857-864. The compounds of the present invention disclosed herein are useful in the prophylaxis or treatment of asthma, and the symptoms thereof.

3. Agitation

Agitation is a well-recognized behavioral syndrome with a range of symptoms, including hostility, extreme excitement, poor impulse control, tension and uncooperativeness (See Cohen-Mansfield J, and Billig, N., (**1986**), Agitated Behaviors in the Elderly. I. A Conceptual Review. J Am Geriatr Soc 34(10): 711-721).

Agitation is a common occurrence in the elderly and often associated with dementia such as those caused by Alzheimer's disease, Lewy Body, Parkinson's, and Huntington's, which are degenerative diseases of the nervous system and by diseases that affect blood vessels, such as stroke, or multi-infarct dementia, which is caused by multiple strokes in the brain can also induce dementia. Alzheimer's disease accounts for approximately 50 to 70% of all dementias (See Koss E, et al., (**1997**), Assessing patterns

of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 11(suppl 2):S45-S50).

An estimated five percent of people aged 65 and older and up to 20 percent of those aged 80 and older are affected by dementia. Of these sufferers, nearly half exhibit behavioral disturbances, such as agitation, wandering and violent outbursts.

Agitated behaviors can also be manifested in cognitively intact elderly people and by those with psychiatric disorders other than dementia

Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging evidence that agents acting at the 5HT2a receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I.R., et al., J Clin Psychiatry 1999 Feb., 60(2):107-115; and Street, J.S., et al., Arch Gen Psychiatry 2000 Oct., 57(10):968-976). The compounds of the invention disclosed herein are useful for treating agitation and symptoms thereof.

4. Add-on therapy to Haloperidol in the treatment of schizophrenia and other disorders:

Schizophrenia is a psychopathic disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by a number of characteristics, psychotic symptoms, progression, phasic development and deterioration in social behavior and professional capability in the region below the highest level ever attained. Characteristic psychotic symptoms are disorders of thought content (multiple, fragmentary, incoherent, implausible or simply delusional contents or ideas of persecution) and of mentality (loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (hallucinations), of emotions (superficial or inadequate emotions), of self-perception, of intentions and impulses, of interhuman relationships, and finally psychomotoric disorders (such as catatonia). Other symptoms are also associated with this disorder. (*See*, American Statistical and Diagnostic Handbook).

Haloperidol (Haldol) is a potent dopamine D2 receptor antagonist. It is widely prescribed for acute schizophrenic symptoms, and is very effective for the positive symptoms of schizophrenia. However, Haldol is not effective for the negative symptoms

of schizophrenia and may actually induce negative symptoms as well as cognitive dysfunction. In accordance with some methods of the invention, adding a 5HT2a inverse agonist concomitantly with Haldol will provide benefits including the ability to use a lower dose of Haldol without losing its effects on positive symptoms, while reducing or eliminating its inductive effects on negative symptoms, and prolonging relapse to the patient's next schizophrenic event.

Haloperidol is used for treatment of a variety of behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS). Further uses include in the prophylaxis or treatment of infantile autism, huntington's chorea, and nausea and vomiting from chemotherapy and chemotherapeutic antibodies. Administration of 5HT2a inverse agonists disclosed herein with haloperidol also will provide benefits in these indications.

For the prophylaxis or treatment of any of these 5HT2A mediated diseases, compounds of Formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the prophylaxis or treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the prophylaxis or treatment of humans.

As indicated above, pharmaceutical compositions for treating 5-HT_{2A} mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active

ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxy-propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to methods known in the art using those suitable dispersing or wetting agents and suspending agents, which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula (I) may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable nonirritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

EXAMPLES

Example 1

General Screening Paradigm: Selection of Pre-Clinical Candidate Leads.

The "primary" screen designed to directly identify human $5HT_{2A}/5HT_{2C}$ receptor inverse agonists consisted of a membrane-based GTPγS binding assay utilizing membranes prepared from COS7 cells transiently transfected with the constitutively active human 5-HT_{2C} receptor. Candidate compounds (10μM final assay concentration) directly identified as inhibiting ligand-independent receptor-mediated increases in GTPγS binding by greater than 50-75% (arbitrary cut-off value) were considered active "hits". Primary assay hits were then re-tested in the same assay to reconfirm their inverse agonist activity. If primary assay hits were reconfirmed active (50% or greater inhibition), and therefore directly identified as, *e.g.*, an inverse agonist, so-called "directed libraries" could be created, *i.e.*, additional candidate compounds were synthesized based upon the structures of the reconfirmed hits (geared towards, *e.g.*, improvement in the characteristics of the compounds) whereby the directed library compounds were then evaluated for the ability to compete for radioligand binding to both mutant human $5HT_{2C}$ (AP-1) and native 5-HT_{2C} receptors and radioligand binding to mutant and endogenous $5HT_{2A}$ receptors. Because these directed library candidate compounds were based upon

the structures of compounds that were directly identified from the membrane-based GTPγS binding assay, the directed library compounds were not re-tested in the membrane-based GTPγS binding assay but rather were then confirmed via the radioligand binding analyses. The radioligand binding analysis tests were initially performed at 10μM test compound in triplicate and if the compound inhibited radiolabeled binding by 50% or more, the analysis was followed by an eight concentration radioligand competitive binding evaluation (triplicate determinations at each test compound concentration) to determine Ki values. The last step in secondary assay evaluation was to determine if test compounds were capable of inhibiting ligand-independent mutant 5-HT_{2A} (AP-3) receptor-mediated accumulation of inositol phosphates (*e.g.*, IP, IP_2, IP_3). This evaluation involved initial testing of compound at 10μM in triplicate and if compound inhibited inositol phosphate accumulation by 50% or more, this analysis was followed by an eight concentration (triplicate determinations at each test compound concentration) IC_{50} determination. This final assay confirms that the directly identified compounds retained inverse agonist properties.

Example 2

Constitutively Activated Human $5HT_{2C}$ Receptor (AP-1), Mediated Facilitation of GTPγS Binding to COS7 Membranes.

Primary screening assays measuring GTPγS binding to membranes prepared from COS7 cells transiently transfected with human mutated 5HT2C receptor (AP-1) were used to directly identify inverse agonists in screening libraries (Tripos, Inc.). Candidate compound screens were performed in a total assay volume of 200 μl using scintillant-coated Wallac Scintistrip™ plates. The primary assay was comprised of the following chemicals (at indicated final assay concentrations): 20 mM HEPES, pH 7.4, 100 mM NaCl, 20 mM $MgCl_2$, 0.2% saponin, 0.2 mM ascorbic acid, 1 μM GDP, 0.3 nM GTPγ^{35}S, and 12.5 μg of the above defined membranes. Incubations were performed for 60 minutes at ambient room temperature. The binding assay incubation was terminated by centrifugation of assay plates at 4,000 rpm for 15 minutes, followed by rapid aspiration of the reaction mixture and counting in a Wallac MicroBeta™ scintillation counter.

Primary screening of candidate compounds initially involved testing of 72 test compounds per assay plate (96-well plates were utilized), at a final assay concentration of 10 μM candidate compound, in single replicates. A total of sixteen wells of each plate were dedicated for an eight-concentration clozapine (a confirmed 5HT2C/2A inverse agonist) dose response curve (duplicate determinations at each concentration). Finally, a total of five assay wells of each plate were dedicated to define the negative control (AP-1 receptor expressing membranes without addition of candidate compounds) and three wells from each plate to define the positive control (membranes without AP-1 receptor).

Reconfirmation experiments involve re-testing candidate compounds in the same assay described above, except that candidate compounds were evaluated in triplicate, thus allowing evaluation of 24 compounds per 96-well assay plate. Similar to the primary assay plates, an eight-concentration clozapine dose response curve (duplicate determinations at each concentration) and the same negative and positive control wells were also included within each 96-well plate.

Example 3

Competition Studies for directly identified compounds: Mutated Human $5HT_{2C}$ Receptor (AP-1).

Radioligand binding competition experiments were performed in a total assay volume of 200 μl using standard 96-well microtiter plates. The final assay ingredients consisted of assay buffer (20 mM HEPES and 10 mM $MgCl_2$), 1nM (^{3}H)mesulergine, and 50 μg of membranes (COS7 with AP-1 as defined above). Nonspecific (^{3}H)mesulergine binding was defined in the presence of 100 μM mianserin. Incubations were performed for 1 hour at 37°C. Receptor bound radioligand was resolved from free radioligand by rapid filtration of the assay mixture over a Wallac Filtermat™ Type B filter, followed by washing with ice-cold assay buffer using a Skatron™ cell harvester. Radioactivity was counted using a Wallac 1205 BetaPlate™ counter. Each assay plate contained five negative control wells (membranes expressing receptor and no candidate compound addition) and three positive control wells (each containing 100 μM mianserin). For one-concentration tests, candidate compounds were diluted into assay buffer and screened at a final concentration of 10 μM, in triplicate. For IC_{50}

determinations, candidate compounds were diluted in assay buffer and eight different concentrations were evaluated, in triplicate. A total of 16 wells were designated for an eight-concentration mianserin dose response curve evaluation for both assays. The same assay conditions were also used to evaluate competition of test compound for radioligand binding to membranes expressing native 5-HT_{2C} receptor.

Example 4

Competition Studies, Wild Type Human 5HT2A Receptor.

Radioligand binding competition experiments were performed in a total assay volume of 200 µl using standard 96-well microtiter plates. The final assay ingredients comprised assay buffer (20 mM HEPES and 10mM $MgCl_2$), 1nM (^{3}H)LSD, and 50 µg of the above-defined membranes (COS7 with AP-1). Nonspecific (^{3}H)LSD binding was defined in the presence of 100 µM serotonin. Incubations were performed for 1 hour at 37° C. Receptor bound radioligand was resolved from free radioligand by rapid filtration of the assay mixture over a Wallac Filtermat™ Type B filter, followed by washing with ice-cold assay buffer using a Skatron™ cell harvester. Radioactivity was counted using a Wallac 1205 BetaPlate™ counter. Each assay plate contained five negative control wells (membranes expressing receptor and no candidate compound addition) and three positive control wells (containing 100 µM mianserin). For one-concentration tests, candidate compounds were diluted into assay buffer and screened at a final concentration of 10 µM in triplicate. For IC_{50} determinations, candidate compounds were diluted in assay buffer and eight different concentrations were evaluated in triplicate. A total of 16 wells were designated for an eight-concentration serotonin dose response curve evaluation for both assays. The same assay conditions were also used to evaluate competition of test compound for radioligand binding to membranes expressing native 5-HT_{2A} receptor.

SYNTHESIS

The following methods apply to synthesis disclosed herein: HPLC-method A: Column: Luna C8, 150 x 4.6 mm, 3 µm SLC-56, with pre-column; Detection: 260 nm; Temperature: 30 °C; Flow rate: 1.5 ml / min; Run time: 21 min; Post time: 8 min;

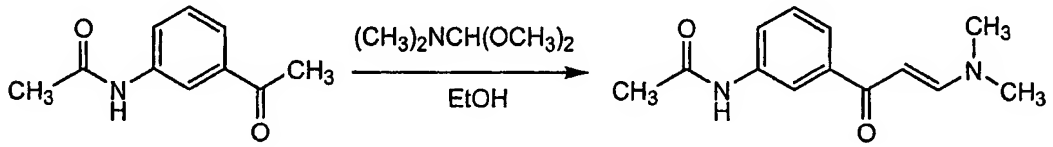
Injection volume: 5 µl; Solvents: A: 5 mmol NH_4-acetate in water, B: 5 mmol NH_4-acetate in water / acetonitrile 2 : 8 (v/v); and

Time:	min.	% A
	0	80%
	20	60%
	21	20%.

GC-method A: used specifically for Compounds (4), (5), (7), (8), Column: HP-5 (crosslinked Ph Me-siloxane); Initial temp.: 50 °C; Initial time: 2 min; Heating rate: 10 °C / min; Final temp.: 250 °C; and Final time: 10 min.

Example 5

Synthesis of 3-Dimethylamino-1-((3′-acetamino)-phenyl)-2-propen-1-one (2) from 3-Acetamidoacetophenone (1):

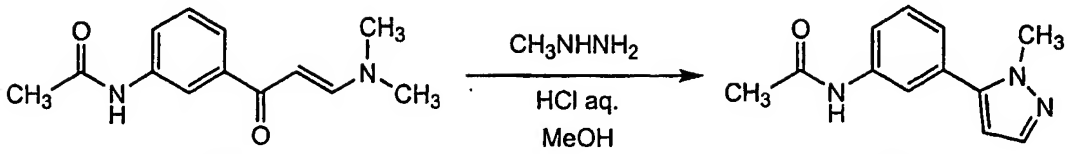


(1) (2)

3-Acetaminoacetophenone (5970 g, 33.7 mol) was placed in a reactor, followed by addition of N,N-dimethylformamide dimethylacetal (6445 g, 54.1 mol, 1.6 equivalents) and anhydrous ethanol (8103 g). The resulting mixture was heated to reflux (internal temp. = 79 to 76°C), whereupon a clear solution was formed. After 9 hours of reflux the conversion was complete (IPC: HPLC). After cooling to 0-5 °C within 1 to 2 hours it was stirred at this temperature overnight, filtered and washed with anhydrous ethanol (4330 g). The crystalline red material was dried in vacuum at 40 to 50 °C to afford enaminone **2** in a yield of 6237 g (80 %) and purity of 99.6 % (HPLC-method A).

Example 6

Synthesis of 5-(3-Acetamidophenyl)-1-methylpyrazole (3) from 3-Dimethylamino-1-((3′-acetamino)-phenyl)-2-propen-1-one (2):



(2) (3)

The reactor was charged with methanol (12404 g) followed by methylhydrazine (1427 g, 31.0 mol, 1.16 equivalents). After cooling to 0 - 5 °C internal temp. 37 % aqueous HCl (8380 g, 85.0 mol, 3.2 equivalents) were added within 30 to 60 min. at an internal temp. of < 10 °C. After cooling to - 10 to 0 °C a suspension of 3-(dimethylamino)-1-(3′-acetamino)-phenyl-2-propen-1-one (6200 g, 26.7 mol) in methanol (44900 g) was added within 45 to 75 min. at an internal temp. of 0 to -10 °C. After completed addition it was warmed to 10 to 15°C within 30 to 60 min. and held for 2 hours at this temp., whereupon less of 1 % of the starting material could be detected by HPLC, a yellow suspension was obtained. Then 25 % aqueous ammonia (4752 g, 69.7 mol) were added within 20 to 40 min., forming a clear orange-colored reaction-mixture (pH 8.1). It was warmed up to 25 to 40 °C of internal temperature and 41.37 kg of solvent were distilled off during 4 to 7 hours, whereupon the product began to crystallize. After cooling to internal temp. = 20 to 30 °C within 45 to 75 min. water (24.90 kg) was added within 10 to 30 min. at int. temp. of 20 to 30°C. It was cooled down to 0 to 5°C within 1 to 2 h and stirred over night (13 h) at this temperature, followed by filtration. The product was washed with pre-cooled water (9270 g). The wet product was dried in vacuum (45 to 60°C) to yield 4938 g (86%) of desired 5-(3-acetamidophenyl)-1-methylpyrazole, purity 99.9 % (HPLC-method A). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H); 7.79 (d, J= 1.2 Hz, 1H); 7.58 (d, J 8.3 Hz, 1H); 7.47 (d, J= 1.9 Hz, 1H); 7.36 (dd, J= 7.5,8.3 Hz, 1H); 7.11 (dd, J= 1.2,7.5 Hz, 1H); 6.29 (d, J= 1.9 Hz, 1H); 3.90 (s, 3H); 2.16 (s, 3H).

Representative isomer ratios are shown in **TABLE 2** utilizing various reaction conditions.

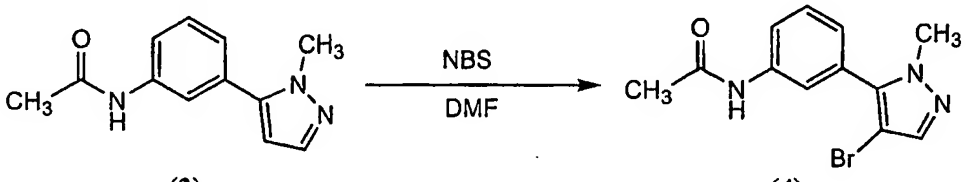
TABLE 2

Exper. No.	Enaminone (mmol)	Solvent (grams)	Equivalents HCl	Equivalents CH_3NHNH_2	Temperature (°C)	Isomer Ratio* 1-Methyl (3):2-Methyl Pyrazole
1	4.1	1.0 g HOAc 6.4 g MeOH	0	1.16	0 to RT	53:47
2	4.1	4.0 g MeOH	1.5	1.16	0 to RT	82:18
3	4.1	4.0 g MeOH	3.0	1.16	RT to 35	82:18
4	12.3	12.0 g MeOH	3.2	1.16	0 to RT	88:12
5	4.1	10.0 g EtOH	3.2	1.16	0 to RT	88:12
6	4.3	4.0 g MeOH	3.0	1.12	0 to RT	88:12
7	172	640.0 g MeOH	3.2	1.16	0 to RT to 40	86:14
8	4.3	17.0 g MeOH	6.0	1.12	0 to RT	91:9

* Isomer Ratios are given as area % determined by HPLC at 250 nm

Example 7

Synthesis of 5-(3-Acetamidophenyl)-4-bromo-1-methylpyrazole (**4**) from 5-(3-Acetamidophenyl)-1-methylpyrazole (**3**)

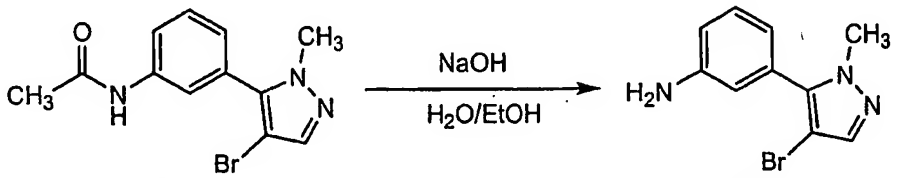


(3) (4)

The reactor was charged with 5-(3-acetamidophenyl)-1-methylpyrazole (1135 g, 5.27 moles) that was suspended in N,N-dimethylformamide (2855 g). A solution of N-bromosuccinimide (963 g, assay 97 %, 5.25 moles) in N,N-dimethylformamide (1870 g) was added at 20 to 30 °C within 40 to 80 min. (IPC 1 hour after addition showed completed reaction). Within 30 to 60 min. it was warmed up to 50 to 60 °C and water (9743 g) was added within 30 to 60 min. at int. temp. = 50 to 60 °C. It was cooled down to 0 to 5°C within 2 to 3 h and held at this temp. for 30 to 60 min., followed by filtration and washing of the crystalline material with water (5286 g). The product was dried in vacuum (50 to 60 °C), yielding 1432 g (92 %) of the 5-(3-acetamidophenyl)-4-bromo-1-methylpyrazole, purity 99.2 % (HPLC-method A).

Example 8

Synthesis of 5-(3-aminophenyl)-4-bromo-1-methylpyrazole (**5**) from 5-(3-Acetamidophenyl)-4-bromo-1-methylpyrazole (**4**):



(**4**) (**5**)

The reactor was charged with 5-(3′-acetaminophenyl)-4-bromo-1-methyl-*1H*-pyrazole **4** (184 g, 0.62 mol), followed by ethanol (464 g) and aqueous NaOH solution (30% by weight) (414 g, 3.10 mol, 5 equivalents). It was heated to reflux whereupon an emulsion was formed. After 17 h of reflux HPLC-analysis showed complete consumption of starting material. It was cooled to an internal temp. of 50 to 70 °C and ethanol was evaporated under reduced pressure until 603 g of reaction mixture were left. Diisopropyl ether (1446 g) was added and after stirring for 30 to 60 min. at an internal temp. of 55 to 60 °C the phases were separated. The organic layer was cooled down to 0 - 5 °C with stirring within 1 to 2 h and seeded at 44 °C. It was stirred for further 30 to 60 min. at 0 to 5 °C and filtered. The product was dried in vacuum at 40 to 50 °C, yielding 96.8 g (61 %) of 5-(3-aminophenyl)-4-bromo-1-methylpyrazole, purity 98.1 % (HPLC-method A). By evaporation of the mother liquor a second crop of product (55 g, 35 %) could by isolated. Thus a total yield of 96 % has been obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s 1H); 7.26 (dd; J 7.8 Hz, 1H); 6.72 - 6.77 (m, 2H); 6.68 (dd; J 1.8 Hz, 1H); 3.80 (s, 3H).

Shown in **TABLE 3** is the time course for the acid hydrolysis of 5-(3-Acetamidophenyl)-4-bromo-1-methylpyrazole (**4**) to 5-(3-aminophenyl)-4-bromo-1-methylpyrazole (**5**). The reaction was conducted as follows: a mixture of 5-(3-acetamidophenyl)-4-bromo-1-methylpyrazole (**4**) as the hydrobromide (1.50 g, 4.0 mmoles), conc HCl (0.80 g, 8 mmoles) in ethanol (3.1 g) and water (1.4 g) was heated to reflux. Samples were taken at various time points and analyzed by HPLC.

TABLE 3

Time (hr)	Starting Material Compound (4) (%)	Product Compound (5) (%)	Unbrominated Amine (%)	Dibrominated Amine (Minor Isomer, %)	Dibrominated Amine (Major Isomer, %)
1	7.7	85.5	1.7	0.6	2.1
2	0.9	89.7	2.9	0.9	3.0
3	0.4	88.4	3.8	1.2	3.5
4	0.4	86.4	4.7	1.4	4.2
6	0.4	83.0	6.3	1.9	5.3
21	0.3	45.5	22.8	5.1	17.3

In a similar manner, a time course was determined for alkaline hydrolysis. The data are shown in **TABLE 4**. The reaction was conducted as follows: a mixture of 5-(3-acetamidophenyl)-4-bromo-1-methylpyrazole (**4**) as the hydrobromide (1.50 g, 4.0 mmoles) and 30% aqueous NaOH (2.60 g, 20 mmoles) in ethanol (3.0 g) and water (1.25 g) was heated to reflux. Samples were taken at various time points and analyzed by HPLC.

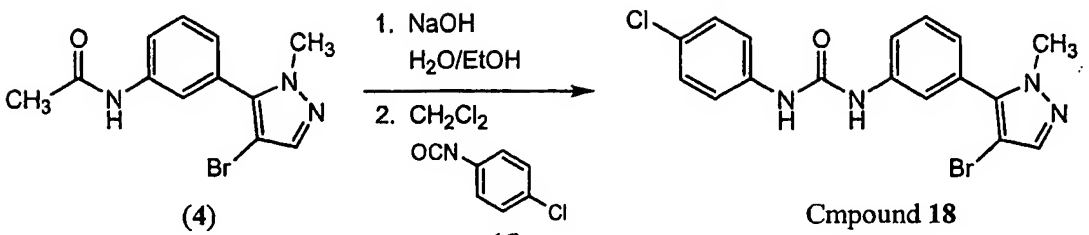
TABLE 4

Time (hr)	Starting Material Compound (4) (%)	Product Compound (5) (%)	Unbrominated Amine (%)	Dibrominated Amine (Minor Isomer, %)	Dibrominated Amine (Major Isomer, %)
2.5	50.3	47.4	1.0	0	0
5	23.0	74.7	1.6	0	0
22	1.2	95.9	2.3	0	0

As related to the study shown in **TABLE 3** and **TABLE 4**, the starting material, Compound (**4**), contained an impurity as the unbrominated amine.

Example 9

Synthesis of N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl) amino) carboxamide (Compound 26, Table 1) from 5-(3-Acetamidophenyl)-4-bromo-1-methylpyrazole (**4**):

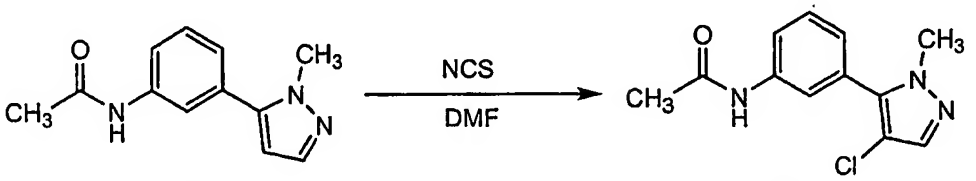


The reactor was charged with 5-(3′-acetaminophenyl)-4-bromo-1-methyl-*1H*-pyrazole 4 (1189 g, 4.04 mol), followed by ethanol (2980 g) and aqueous NaOH solution (30% by weight) (2685 g, 20.1 mol, 5 equivalents). It was heated to reflux whereupon an emulsion was formed. After 16 h HPLC-analysis revealed consumption of starting material. It was cooled to an internal temp. of 40 to 50 °C and ethanol was evaporated under reduced pressure until 1420 g of reaction mixture were left. It was seeded with 5-(3-aminophenyl)-4-bromo-1-methylpyrazole (**5**) and cooled to 20 to 25 °C. The crude product (**5**) was filtered by suction and washed with water (2 x 2300 g). The wet product (**5**) was dissolved in dichloromethane (7475 g). After 10 to 15 min. stirring was stopped and the emulsion was allowed to separate in two phases (10 to 15 min.). The organic layer was isolated and anhydrous sodium sufate (412 g) was added. It was stirred for 10 to 20 min., filtered by suction and washed with dichloromethane (4672 g). To this solution a mixture of 4-chlorophenyl-isocyanate (646 g; 4.20 mol, 1.04 equivalents) and dichloromethane (1645 g) was added within 10 to 20 min. at 20 to 25 °C. After 5 h the suspension of product obtained was cooled to 0 - 5 °C and stirred for further 40 to 80 min. at this temperature. It was filtered by suction (1.5 h necessary) and washed with dichloromethane (3211 g). The product was dried at 40 to 45 °C, yielding 1260 (77 %) of Compound 18, purity 98.9 % (HPLC-method A).

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.92 (s, 1H); 8.89 (s, 1H); 7.65 (s, 1H); 7.63 - 7.62 (dd, J = 1.4, 2.0 Hz, 1H); 7.59 - 7.55 (ddd, J = 1.2, 2.0, 8.2 Hz, 1H); 7.54 - 7.49 (m, J = 8.9 Hz, 2H); 7.49 - 7.43 (dd, J = 7.6, 8.2 Hz, 1H); 7.35 - 7.30 (m , J = 8.9 Hz, 2H); 7.11 - 7.08 (ddd, J = 1.2, 1.4, 7.6 Hz, 1H), 3.79 (s, 3H). ^{13}C-NMR (300 MHz, DMSO-d_6): δ 152.3; 140.3; 139.8; 138.4; 129.1; 128.5; 128.2; 125.4; 123.0; 119.8; 119.2; 118.9; 92.2; 38.1.

Example 10

Synthesis of 5-(3′-acetylaminophenyl)-4-chloro-1-methyl-*1H*-pyrazole (7) from 5-(3′-acetaminophenyl)-1-methyl-*1H*-pyrazole **3**:



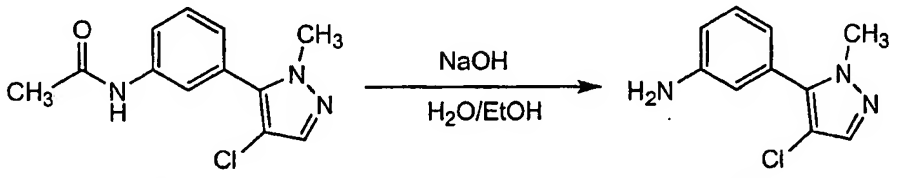
(3) (7)

The reactor was charged with 5-(3′-acetaminophenyl)-1-methyl-*1H*-pyrazole **3** (363.6 g, 1.69 mol) that was suspended in N,N-dimethylformamide (911 g). A solution of N-chloro-succinimide (230.2 g, assay 98 %, 1.69 mol) in N,N-dimethylformamide (750 g) was added at an internal temp. of 51 to 57 °C during a period of 1 to 1.5 h. After stirring for further 2 to 3 h at 53 to 63 °C IPC showed absence of starting material. To the clear solution water (4811 g) was added within 30 to 60 min. at an internal temp. of 55 to 60 °C, followed by cooling to int. temp of 0 to 5 °C within 2 to 3 h. After stirring for further 30 to 60 min. at this temperature it was filtered and washed with water (1689 g). The product was dried in vacuum (50 to 60 °C), yielding 400 g (96%) of the chloro-pyrazole **7** (purity 100 %, HPLC-method AR116081).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H); 7.64 (s, 1H), 7.58 (d, J 8.4 Hz, 1H), 7.49 (s, 1H), 7.42 (dd, J 7.6,8.4 Hz, 1H), 7.14 (d, J 7.6 Hz, 1H), 3.79 (s, 3H), 2.18 (s, 3H).

Example 11

Synthesis of 5-(3′-aminophenyl)-4-chloro-1-methyl-*1H*-pyrazole (**8**) from 5-(3′-acetylaminophenyl)-4-chloro-1-methyl-*1H*-pyrazole (7):



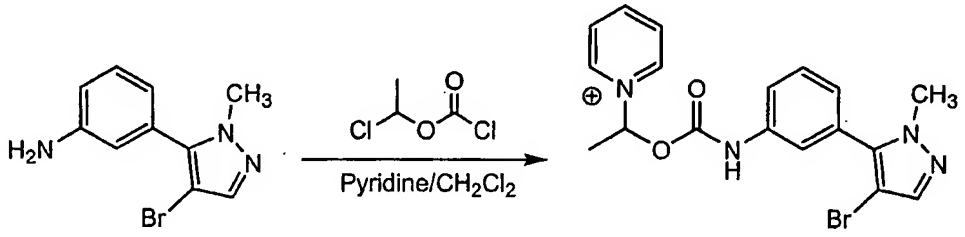
(7) (8)

The reactor was charged with 5-(3′-acetaminophenyl)-4-chloro-1-methyl-*1H*-pyrazole **7** (397 g, 1.59 mol) followed by ethanol (995 g) and aqueous NaOH solution (30% by weight) (1056 g, 7.92 mol, 5 equivalents). It was heated to reflux whereupon a yellowish emulsion was formed. After 5.2 h of reflux HPLC analysis showed

consumption (< 0.5 % left) of starting material. It was cooled to an internal temp. of 50 to 70 °C and ethanol was evaporated at a pressure of 90 to 130 mbar until 1462 g of reaction mixture were left. Diisopropyl ether (684 g) was added with efficient stirring , after separation of phases the aqueous layer was retransferred into the reactor and again extracted with diisopropyl ether (150 g). Both organic layers were combined and seeded followed by cooling of the suspension to - 8 to -12 °C of internal temp. within 1 to 2 h. It was stirred over night at this temperature. The product was filtered an dried over night in vacuum at 40 to 50 °C, yielding 168.4 g (51 %) of the amine **8**.

Example 12

Synthesis of Pyridinium Salt (**28**) from 5-(3-aminophenyl)-4-bromo-1-methylpyrazole (**5**):

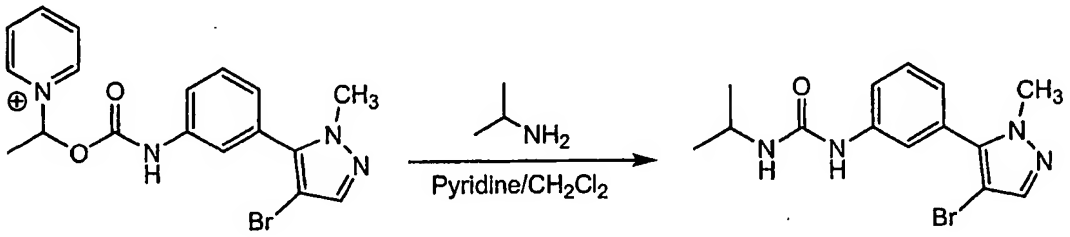


(**5**) (**28**)

Pyrazole (**5**) (3.07g, 12.2 mmol) was dissolved in anhydrous CH_2Cl_2 (45 mL) and treated with pyridine (2.96 mL, 36.6 mmol). The solution was stirred at room temperature. After allowing it to stir for five minutes, 1-chloroethyl chloroformate (1.45 mL, 13.4 mmol) was added drop by drop. After 4.5 hours at room temperature, the reaction was shown to be incomplete by TLC and LC/MS. An additional equivalent of the chloroformate (1.32 mL, 12.2 mmol) was added. Once the reaction went to completion (after another two hours,) it was worked up with EtOAc (2 x 100 mL) and Brine (2 x 100 mL). Upon being treated to this work up, the pyridinium salt precipitated out of solution into the aqueous layer in a 57-80% yield: LCMS m/z (%) = 401 ($M+H^{79}Br$, 14), 403 ($M+H^{81}Br$, 10). ^1H NMR (400 MHz. CD_3OD) σ 9.27 (d, 2H), 8.71 (t, 1H), 8.23 (t, 2H), 7.52 (s, 1H), 7.50 (s, 1H), 7.47 (t, 1H), 7.15 (d,1H), 7.11 (q, 1H), 3.76 (s, 3H), 2.03 (d, 3H).

Example 13

Synthesis of N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)(isopropylamino) carboxamide (**29**) from pyridinium salt (**28**):

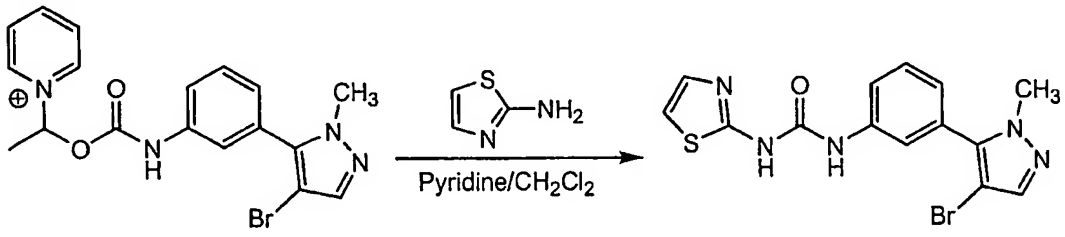


(**28**) (**29**)

Pyridinium salt (**2**), from Example 12, was dissolved in anhydrous CH_2Cl_2 (3 mL). The solution was stirred and treated with pyridine (118 μL, 1.46 mmol). The solution was stirred at room temperature for five minutes. Then the solution was heated to 39°C and isopropylamine (45.5 μL, 0.53mmol) was added drop by drop. After two hours the reaction was complete. The reaction mixture was quenched with 5 mL 1N HCl and the organic layer was extracted with EtOAc. The organic layer was then dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure, yielding 40.1 mg (24%) of AR145253: LCMS m/z (%) = 337 ($M+H^{79}Br$, 100), 339 ($M+H^{81}Br$, 90). ^1H NMR (400 MHz. $CDCl_3$) σ 7.53 (s, 1H), 7.43 (m, 3H), 7.08 (d, 1H), 4.02 (m, 1H), 3.83 (s, 3H), 1.20 (d, 6H).

Example 14

Synthesis of N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)(thiazol-2-yl amino) carboxamide (**30**) from pyridinium salt (**28**):



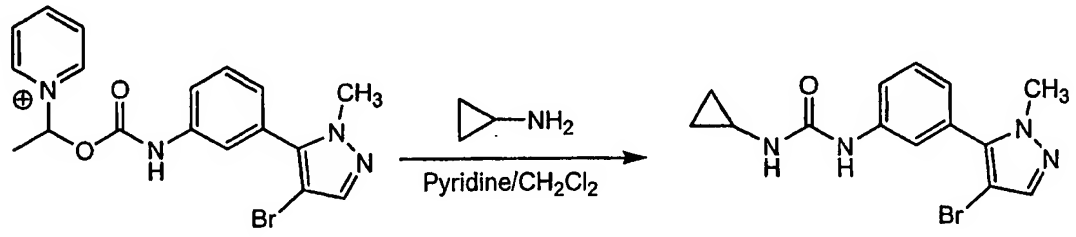
(**28**) (**30**)

Pyridinium salt (**28**), from Example 12, was treated with 2-Aminothiazole, in a similar manner to as described in Example 12 for N-(3-(4-bromo-2-methylpyrazole-3-

yl)phenyl)(isopropylamino) carboxamide (29), to provide N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)(thiazol-2-yl amino) carboxamide in a yield of 22%: LCMS m/z (%) = 380 ($M+H^{81}Br$, 100), 378 ($M+H^{79}Br$, 72). ^1H NMR (400MHz. $CDCl_3$) σ 7.72 (d,1H), 7.60 (d,1H), 7.48 (d,1H), 7.44 (s, 1H), 7.31 (s, 1H), 7.22 (t,1H), 7.07 (d, 1H), 3.83 (s, 3H).

Example 15

Synthesis of N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)(cyclopropylamino) carboxamide (31) from pyridinium salt (28):

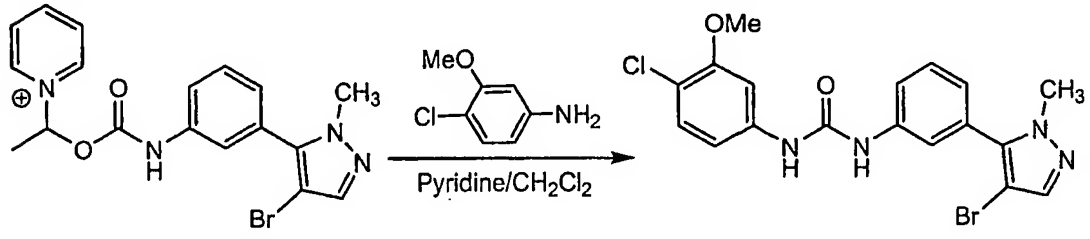


(28) (31)

Pyridinium salt (28), from Example 12, was treated with cyclopropyl amine, in a similar manner as described in Example 12, to provide N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)(cyclopropylamino) carboxamide in a yield of 22%: LCMS m/z (%) = 337 ($M+H^{79}Br$, 100), 339 ($M+H^{81}Br$, 97). ^1H NMR (400MHz. $CDCl_3$) σ 7.55 (d, 1H), 7.47 (s, 1H), 7.465 (s, 1H), 7.461 (t, 1H), 7.10 (d, 1H), 3.84 (s, 3H), 0.88 (m, 2H), 0.67 (m, 2H).

Example 15

Synthesis of N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)((4-chloro-3-methoxyphenyl)amino) carboxamide (32) from pyridinium salt (28):



(28) (32)

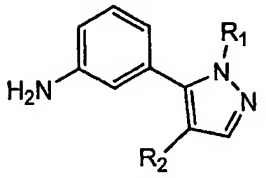
Pyridinium salt (**28**), from Example 12, was treated with 4-chloro-3-methoxyaniline, in a similar manner to as described in Example 12, to provide N-(3-(4-bromo-2-methylpyrazole-3-yl)phenyl)((4-chloro-3-methoxyphenyl)amino) carboxamide in a yield of 60%: LCMS m/z (%) = 435 ($M+H^{79}Br$, 97), 437 ($M+H^{81}Br$, 100).

Throughout this application, various publications, patents and published patent applications are cited. The disclosures of these publications, patents and published patent applications referenced in this application are hereby incorporated by reference in their entirety into the present disclosure. Modifications and extension of the disclosed inventions that are within the purview of the skilled artisan are encompassed within the above disclosure and the claims that follow.

CLAIMS

We Claim:

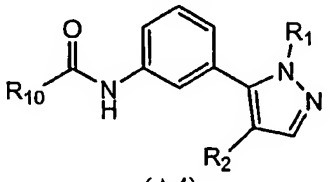
1. A process for making a compound of Formula (A5):



(A5)

the process comprising:

hydrolyzing a compound of Formula (A4):



(A4)

with an alkali metal hydroxide in an hydrolyzing solvent to yield a compound of Formula (A5); wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{10} is C_{1-6} alkyl.

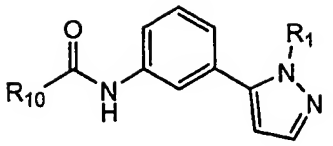
2. The process according to claim 1 wherein the alkali metal hydroxide is sodium hydroxide.

3. The process according to claim 2 wherein the hydrolyzing solvent is aqueous ethanol.

4. The process according to claim 3 wherein the hydrolyzing step is conducted at a temperature between about 60°C to about 80°C.

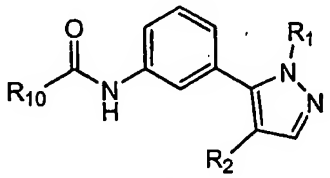
5. The process according to claim 1 comprising the steps of:

halogenating a compound of Formula (A3)



(A3)

with a halogenating reagent in a halogenating solvent to yield a compound of Formula (A4);



(A4) ; and

hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5); wherein R_{10} is C_{1-6} alkyl.

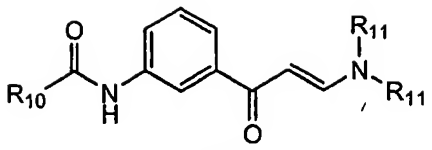
6. The process according to claim 5 wherein the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide.

7. The process according to claim 6 wherein the halogenating reagent is N-bromosuccinimide and the halogenating solvent is N,N-dimethylformamide, and the halogenating step is conducted at a temperature between about 20°C to about 60°C.

8. The process according to claim 7 wherein the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted at a temperature between about 60°C to about 80°C.

9. The process according to claim 1 comprising the steps of:

cyclizing a compound of Formula (A2):



(A2)

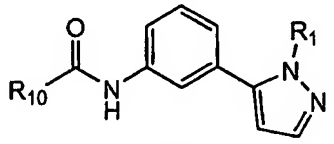
with a compound of Formula (B2):

R_1—$NHNH_2$

(B2)

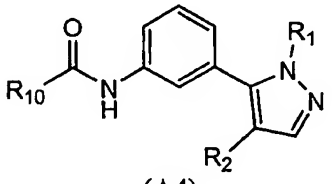
R_1 is C_{1-2} alkyl;

the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (A3);



(A3) ; and

halogenating a compound of Formula (A3) with a halogenating reagent in a halogenating solvent to yield a compound of Formula (A4);



(A4) ;

hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5); wherein R_1 is C_{1-2} alkyl; R_{10} is C_{1-6} alkyl; and R_{11} is C_{1-3} alkyl.

10. The process according to claim 9 further comprising a cyclizing acid in the cyclizing step.

11. The process according to claim 10 wherein the cyclizing acid is hydrochloric acid.

12. The process according to claim 11 wherein the compound of Formula (B2) is methyl hydrazine.

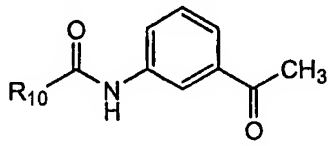
13. The process according to claim 12 wherein the cyclization solvent is methanol.

14. The process according to claim 13 wherein the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide, the halogenating solvent is N,N-dimethylformamide, and the halogenating step is conducted at a temperature between about 20°C to about 60°C.

15. The process according to claim 14 wherein the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted at a temperature between about 60°C to about 80°C.

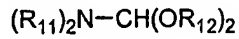
16. The process according to claim 1 comprising the steps of:

condensing a compound of Formula (**A1**):



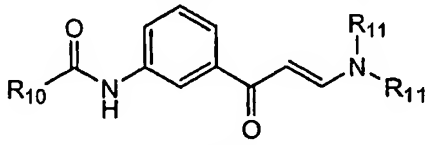
(**A1**)

with a compound of Formula (**B1**):



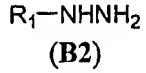
(**B1**)

the condensing step is optionally conducted in an condensing solvent to yield a compound of Formula (**A2**):



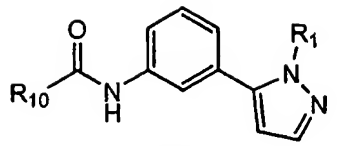
(**A2**) ;

cyclizing a compound of Formula (**A2**) with a compound of Formula (**B2**):



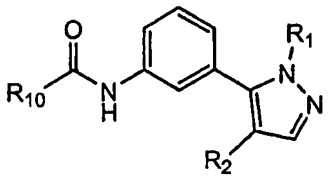
(**B2**)

the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (**A3**):



(A3) ;

halogenating a compound of Formula (A3) with a halogenating reagent in a halogenating solvent to yield a compound of Formula (A4);



(A4) ; and

hydrolyzing a compound of Formula (A4) with an alkali metal hydroxide in an aqueous hydrolyzing solvent to yield a compound of Formula (A5); wherein R_1 is C_{1-2} alkyl; R_{10} is C_{1-6} alkyl, R_{11} is C_{1-3} alkyl; and R_{12} is C_{1-6} alkyl or alkylaryl; or both R_{12} groups together form a 5 or 6 membered heterocyclic ring.

17. The process according to claim 16 wherein the compound of Formula (B1) is *N,N*-dimethylformamide dimethyl acetal.

18. The process according to claim 17 wherein the condensing solvent is ethanol and the condensing step is conducted at a temperature of about 25°C to about 95°C.

19. The process according to claim 18 wherein the condensing step is conducted at a temperature of about 70°C to about 80°C.

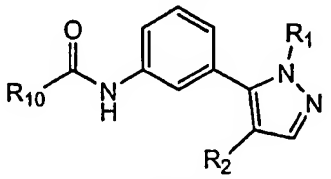
20. The process according to claim 19 further comprising a cyclizing acid in the cyclizing step and the cyclizing acid is hydrochloric acid.

21. The process according to claim 20 wherein the compound of Formula (B2) is methyl hydrazine and the cyclization solvent is methanol.

22. The process according to claim 21 wherein the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide, the halogenating solvent is N,N-dimethylformamide, and the halogenating step is conducted at a temperature between about 20°C to about 60°C.

23. The process according to claim 22 wherein the alkali metal hydroxide is sodium hydroxide, the hydrolyzing solvent is aqueous ethanol, and the hydrolyzing step is conducted at a temperature between about 60°C to about 80°C.

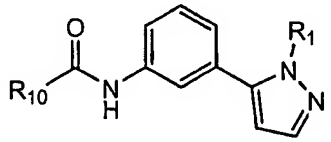
24. A process for making a compound of Formula (**A4**):



(**A4**)

the process comprising the steps of:

halogenating a compound of Formula (**A3**)



(**A3**)

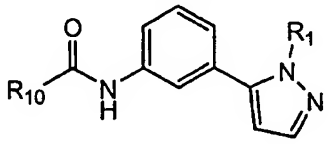
with a halogenating reagent in a halogenating solvent to yield the compound of Formula (**A4**); wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{10} is C_{1-6} alkyl.

25. The process according to claim 24 wherein the halogenating reagent is N-bromosuccinimide or N-chlorosuccinimide.

26. The process according to claim 25 wherein the halogenating reagent is N-bromosuccinimide and the halogenating solvent is N,N-dimethylformamide.

27. The process according to claim 26 wherein the halogenating step is conducted at a temperature between about 20°C to about 60°C.

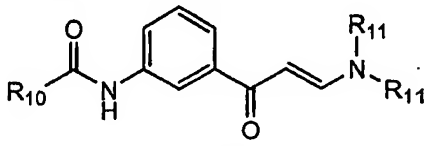
28. A process for making a compound of Formula (**A3**):



(A3)

the process comprising the steps of:

cyclizing a compound of Formula (**A2**):



(A2)

with a compound of Formula (**B2**):

R_1—$NHNH_2$

(B2) ;

the cyclizing step is optionally conducted in a cyclizing solvent to yield the compound of Formula (**A3**); wherein R_1 is C_{1-2} alkyl; R_{10} is C_{1-6} alkyl; and R_{11} is C_{1-3} alkyl.

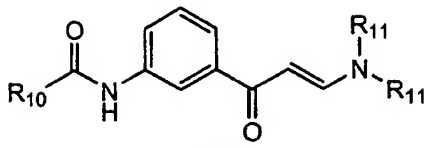
29. The process according to claim 28 further comprising a cyclizing acid in the cyclizing step.

30. The process according to claim 29 wherein the cyclizing acid is hydrochloric acid.

31. The process according to claim 30 wherein the compound of Formula (**B2**) is methyl hydrazine.

32. The process according to claim 31 wherein the cyclization solvent is methanol.

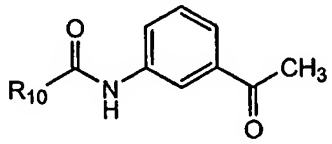
33. A process for making a compound of Formula (**A2**):



(A2)

the process comprising the steps of:

condensing a compound of Formula (A1):



(A1)

with a compound of Formula (B1):

$(R_{11})_2N-CH(OR_{12})_2$

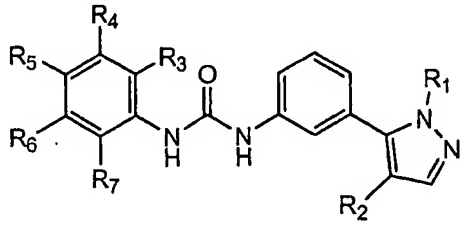
(B1)

the condensing step is optionally conducted in an condensing solvent to yield a compound of Formula (A2); wherein R_{10} is C_{1-6} alkyl; R_{11} is C_{1-3} alkyl; and R_{12} is C_{1-6} alkyl or alkylaryl; or both R_{12} groups together form a 5 or 6 membered heterocyclic ring.

34. The process according to claim 33 wherein the compound of Formula (B1) is *N,N*-dimethylformamide dimethyl acetal.

35. The process according to claim 34 wherein the condensing solvent is ethanol and the condensing step is conducted at a temperature of about 25°C to about 95°C.

36. A process for making a compound of Formula (I):



(I)

wherein:

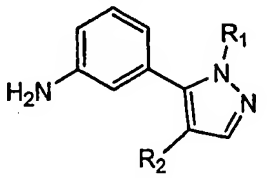
R_1 is C_{1-2} alkyl;

R_2 is Cl or Br; and

R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H;

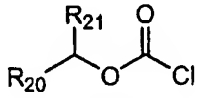
the process comprising:

reacting a compound of Formula (**A5**):



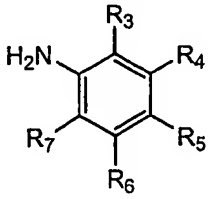
(**A5**)

with a substituted alkyl chloroformate of Formula (**B6**):



(**B6**)

and an organic base in a non-reactive solvent to give an intermediate; and coupling the intermediate with a compound of Formula (**A8**):



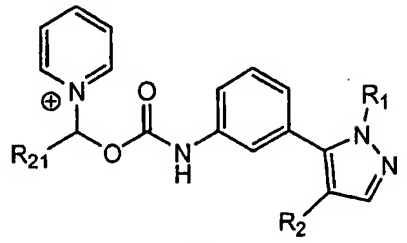
(**A8**)

to yield the compound of Formula (**I**); wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; and wherein R_{20} is a Cl, Br, I, mesylate or tosylate; R_{21} is a C_1-C_8 alkyl.

37. The process according to claim 36 wherein the organic base is pyridine.

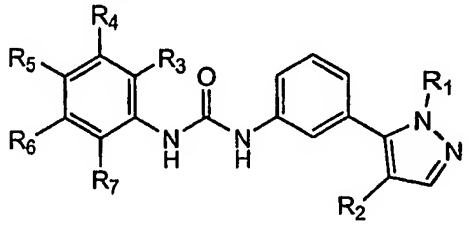
38. The process according to cliam 37 wherein the non-reactive solvent is methylene chloride.

39. The process according to claim 38 wherein the intermediate is Formula (**C2**):



(**C2**)

40. A process for making a compound of Formula (**I**):



(**I**)

wherein:

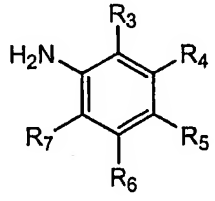
R_1 is C_{1-2} alkyl;

R_2 is Cl or Br; and

R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H;

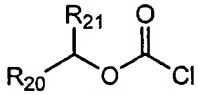
the process comprising:

reacting a compound of Formula (**A8**):



(**A8**)

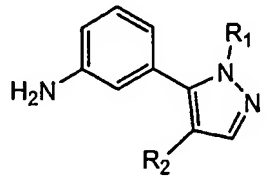
with a substituted alkyl chloroformate of Formula (**B6**):



(**B6**)

wherein R_{20} is a Cl, Br, I, mesylate or tosylate; R_{21} is a C_1-C_8 alkyl;

and an organic base in a non-reactive solvent to give an intermediate; and coupling the intermediate with a compound of Formula (**A5**):



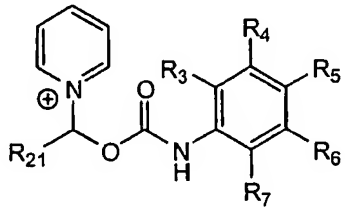
(**A5**)

to yield the compound of Formula (**I**); wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least R_3, R_4, R_5, R_6 and R_7 is not H.

41. The process according to claim 40 wherein the organic base is pyridine.

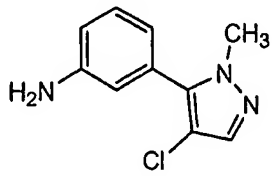
42. The process according to claim 41 wherein the non-reactive solvent is methylene chloride.

43. The process according to claim 42 wherein the intermediate is Formula (**C4**):

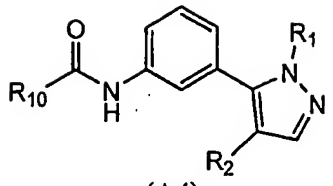


(**C4**)

44. A compound of the Formula:



45. A compound of Formula (**A4**):

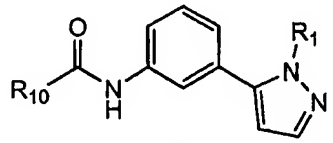


(A4)

wherein R_1 is C_{1-2} alkyl; R_2 is Cl or Br; and R_{10} is C_{1-6} alkyl.

46. The compound according to claim 45 wherein R_1 and R_{10} are both CH_3, and R_2 is Br.

47. A compound of Formula (A3):

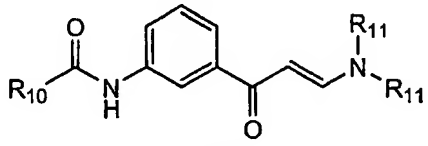


(A3)

wherein R_1 is C_{1-2} alkyl; and R_{10} is C_{1-6} alkyl.

48. The compound according to claim 47 wherein R_1 and R_{10} are both CH_3.

49. A compound of Formula (A2):

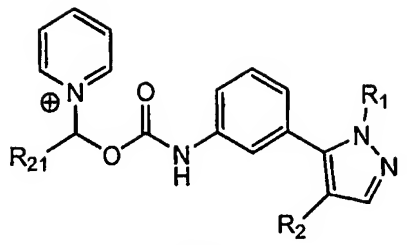


(A2)

wherein R_{10} is C_{1-6} alkyl; and R_{11} is C_{1-3} alkyl.

50. The compound according to claim 49 wherein R_{10} and R_{11} are both CH_3.

51. A compound of the formula:



(C2)

wherein:

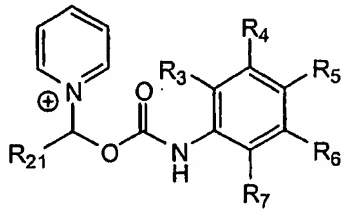
R_1 is C_{1-2} alkyl;

R_2 is Cl or Br; and

R_{21} is C_1-C_8 alkyl.

52. The compound according to claim 51 wherein R_1 is CH_3; R_2 is Br; and R_{21} is CH_3.

53. A compound of the formula:



(C4) ;

wherein R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, halogen, or haloalkyl; provided that at least one is not H; and R_{21} is C_1-C_8 alkyl.

54. The compound according to claim 53 wherein R_3, R_4, R_5, R_6 and R_7 are each independently selected from H, F or Cl; and R_{21} is CH_3.